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SOME USES AND ABUSES OF CHEMOTHERAPY IN PNEUMONIA*

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THERE can now be little doubt concerning the value of the newer sulfonamide drugs in the therapy of pneumonia. Almost every physician has had some personal experience to demonstrate the effectiveness of sulfapyridine or sulfathiazole in this disease. There are, however, a number of important practical problems that require elucidation on the basis of recent accumulated experience. In this paper, we present our views on some of these problems.

GENERAL CONSIDERATIONS

Choice of sulfonamide drugs in the treatment of pneumonia. The three compounds that have proved effective and have been used widely in the treatment of bacterial infections are sulfanilamide, sulfapyridine and sulfathiazole; a fourth drug, sulfadiazine, is now being evaluated. In the choice of a drug for use in the treatment of acute pulmonary infection, one thinks primarily of its effectiveness against the pneumococcus, which is the most frequent causative agent in pneumonia. However, when chemicals are equally effective against pneumococcus and other organisms that may cause pneumonia, other things being equal, the drug with the widest range of effectiveness is the one of choice. On the other hand, the drug of choice between compounds of similar efficacy is obviously the one offering the least likelihood of producing toxic effects.

In Table 1, we have summarized our evaluation of the toxicity of these four drugs, as well as of their relative effectiveness against the common causative agents of pneumonia. This is based on our own experience and on the clinical and experimental data available in the literature. Obviously, sulfanilamide should not be used except in hemolytic streptococcus pneumonias, and then only when other drugs are not well tolerated. It is also apparent that until sulfadiazine becomes available,§ the drug of choice in the treatment of pneumonia is sulfathiazole. Recent experience indicates that sulfadiazine has a wider range of effectiveness and is much less toxic than sulfathiazole; it is therefore our present choice for the treatment of pneumonia. The details of our studies with this drug are given elsewhere.[1]

TABLE 1. *Summary of the Relative Toxicity and Efficacy of Four Sulfonamide Drugs in Infections with the Most Important Organisms Associated with Pneumonia.*

DRUG	RELATIVE TOXICITY	RELATIVE EFFECTIVENESS IN CERTAIN INFECTIONS			
		Pneumococcus	*Streptococcus hemolyticus*	*Staphylococcus aureus*	Friedländer's bacillus
Sulfanilamide	+++	+	++	0	0
Sulfapyridine	+++	+++	++	+	+?
Sulfathiazole	++	+++	+	+++	+
Sulfadiazine	+	+++	+++	+++	++

Route of administration. Because the danger of renal complications is greater with parenteral chemotherapy, the oral route is always to be preferred. However, an initial intravenous dose of the sodium salt of the drug to be used is indicated in patients who are extremely ill, in those who are comatose, and in those with severe vomiting. Usually, a 5-gm. dose is given to the average adult, and may be followed by 2 or 3 gm. after about six hours. Although it is ordinarily recommended that this be given in distilled water as a 5 per cent solution, we prefer to give it intravenously as a 0.5 to 2 per cent¶ solution in physiologic saline. For subsequent parenteral administration,

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§Sulfadiazine has now been released for sale under the Federal Food, Drugs and Cosmetic Act.

¶Higher concentrations tend to precipitate out of solution from physiologic saline.

we prefer the subcutaneous injection of the sodium salts of the sulfonamides given in 0.5 or 0.75 per cent solution in saline. The daily dose may be divided into three or two doses, given at intervals of eight or twelve hours, respectively. An intravenous or, preferably, a subcutaneous dose of the sodium salt is also indicated in occasional patients in whom the usual oral doses do not bring about an adequate response and in whom the blood level is found to be low, suggesting that there is poor absorption of the drug. In every case in which parenteral therapy is used, it should be discontinued in favor of oral therapy as soon as possible, since the worst renal complications have occurred when parenteral therapy has been maintained too long.

Rectal administration of sulfonamides should not be used in adults. None of the effective drugs except sulfanilamide are absorbed sufficiently from this route to be of value.[2, 3]

Fluids. The total fluid intake should be such as to ensure a urine output of over 1000 cc., and preferably over 1500 cc., daily. It is usually necessary to give 3000 to 3500 cc. of fluid, and parenteral fluids should be given if necessary.

Dosage and duration of treatment. In general, the dosage of each of the effective sulfonamides in pneumonia for the average adult is about the same, namely, an initial dose of 4 gm. followed by 1 gm. every four hours. It is usually sufficient to continue treatment for two to five days after the temperature and pulse have returned to normal and the symptoms of the acute disease have subsided. The longer period is reserved for the severest cases. In pneumonias due to organisms other than the pneumococcus, especially in hemolytic streptococcus or staphylococcal infections and also in all cases with infected purulent complications, drug therapy may be continued for longer periods. It is essential to bear in mind that the serious complications, such as drug fevers, rashes and particularly agranulocytosis, occur with increasing frequency the longer drug therapy is maintained. Rashes and fevers are commonest after the first week and agranulocytosis after the second week of treatment. In general, we prefer to stop therapy abruptly rather than to diminish the dose gradually. When sulfadiazine is used, however, because higher levels in the blood can be maintained with smaller amounts of the drug, the dose may be reduced to 1 gm. every six hours after essential recovery has taken place.

In all cases in which impairment of renal function is suspected, treatment should be undertaken with caution. Urines should be examined and the level of drug determined early in the course of treatment.

In the treatment of patients with pleural complications, it is important to differentiate sterile and infected pleural fluids. For this purpose, thoracentesis is performed, and the fluid obtained is examined for the number and character of the cells and for the presence of organisms in an ordinary stained preparation, and is also cultured. The absence of organisms in the stained smear and the presence of many mononuclear cells are presumptive evidence of a sterile effusion, but this should be verified by culture. In such cases, chemotherapy may safely be discontinued, since sterile fluids are usually absorbed spontaneously. In patients with purulent infected fluids, chemotherapy may be continued for a few days,

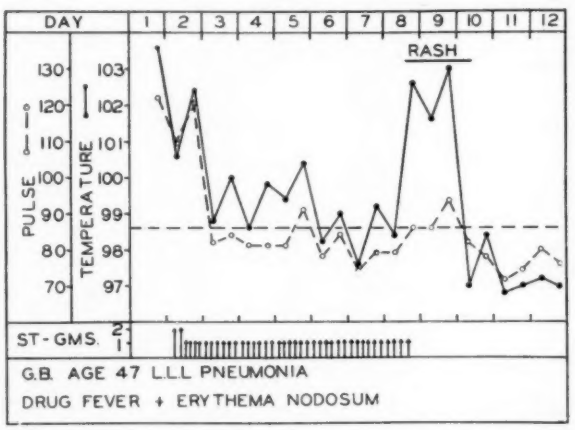
DAY
1 2 3 4 5 6 7 8 9 10 11 12
RASH
PULSE
TEMPERATURE
130 120 110 100 90 80 70
103 102 101 100 99 98 97
ST-GMS.
G.B. AGE 47 LLL PNEUMONIA
DRUG FEVER + ERYTHEMA NODOSUM

FIGURE 1. *Sulfathiazole Fever and Rash.*

In this and the subsequent figures, the following abbreviations are used:

♂ = male; ♀ = female.

SP = *sulfapyridine;* ST = *sulfathiazole;* SD = *sulfadiazine;* NaSD = *sodium sulfadiazine.*

L.L.L. = *left lower lobe;* R.L.L. = *right lower lobe; and so forth.*

C.F. = *pleural fluid.*

PN. I = *pneumococcus, Type 1;* PN. II = *pneumococcus, Type 2; and so forth.*

I.M. = *intramuscular;* I.V. = *intravenous.*

W.B.C. = *leukocytes, thousands per cu.mm.;* R.B.C. = *erythrocytes, millions per cu.mm.*

PMN = *polymorphonuclear leukocytes.*

N.P.N. = *nonprotein nitrogen, mg. per 100 cc.*

Blood culture: 0 = *sterile;* + = *positive for pneumococcus; numbers represent colonies per cc. of blood;* ∞ = *innumerable.*

but operation should be performed for drainage as soon as it is obvious that the infection is not yielding to treatment.

Drug fever. This is a frequent occurrence in patients under sulfonamide therapy and is sometimes difficult to differentiate from postpneumonic complications. Figure 1 shows the chart of a patient with drug fever during the course of chemotherapy. Such drug fever may or may not be

associated with rash and may be accompanied by chills. Frequently, the pulse rate remains relatively low, in spite of the elevation in temperature, and the symptoms of acute pulmonary infection do not recur. The leukocyte count may be somewhat elevated but is usually not very high during the early stages of drug fever. Cases of marked leukocytosis, however, have been noted. The diagnosis of drug fever is justified only when a characteristic rash is present or when the fever subsides within twelve to thirty-six hours after drug therapy is discontinued.

Use of serum in pneumococcal pneumonias. It is now generally agreed that sulfonamide therapy is to be preferred to serum therapy in all except the rare cases in which severe toxic reactions precludes the use of the drugs. Moreover, there is little doubt that the routine use of serum as an adjunct to chemotherapy is unwarranted, since it exposes the patient unnecessarily to the hazards of serotherapy. The differences in clinical response in the great majority of cases do not justify the added expense and effort. The availability of highly effective and relatively nontoxic drugs has now raised the question whether any patients receive sufficient additional benefit from serum to warrant its use as an adjunct to chemotherapy. Doubts concerning the additional value of serum are also based on serologic or statistical comparisons of cases treated with the sulfonamides alone and those in which such treatment is supplemented by serum. We have given long and serious consideration to this problem and believe that a definitive answer cannot be given at this time because of the great difficulty of obtaining conclusive data. Our experience leads us to consider additional serotherapy justified and necessary in individual cases. In general, these include some of the cases with the worst prognosis and those in which adequate treatment with the drug fails to bring about the desired result in a reasonably short time, usually twenty-four to forty-eight hours. In some patients with infected purulent complications, adequate control of the infection may not take place until serotherapy is used, and large amounts of serum are often necessary under these conditions.

Obviously, it is impossible in retrospect to evaluate the relative role of each agent in cases in which both drugs and serum have been used. In the patients who survive, reasonable doubts may be raised about the part that the serum played in their recovery. In some of the fatal cases, it is equally reasonable to raise a question concerning what part the serum or the drug played in the fatal outcome. This is particularly true when untoward reactions to either agent are encountered or when serum is given intravenously in the presence of cardiac or circulatory failure.

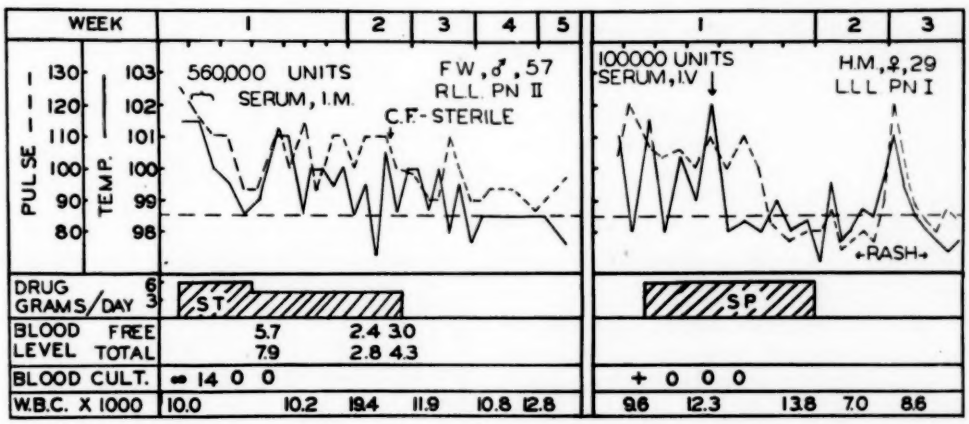

FIGURE 2. *Two Patients in Whom Sulfonamide Therapy Was Supplemented by Antipneumococcus Serum.*

Figure 2 shows the charts of two patients who recovered after receiving serum in addition to chemotherapy. One patient (F. W.) was practically moribund at the time of admission to the hospital, and his blood was heavily invaded before the first dose of sulfathiazole was given. When serum therapy was started on the morning after admission, the patient had shown no signs of clinical improvement, although the bacteremia was partly but not completely controlled. The patient's condition was so poor that it was believed that the shock of intravenous serum therapy would be sufficient to turn the balance against him. Serum was therefore given intramuscularly, and no reactions resulted. The bacteremia was rapidly controlled, and a balance of antibodies was established within twelve hours after the first intramuscular dose. Although those who attended this patient agreed at the time that serum con-

tributed materially to the patient's survival, it cannot be stated with any degree of assurance that this patient would not have survived under sulfathiazole therapy alone.

It was believed that the other patient (H. M.) was not responding favorably after two days on full doses of sulfapyridine, whereas a dramatic response followed the administration of serum. In

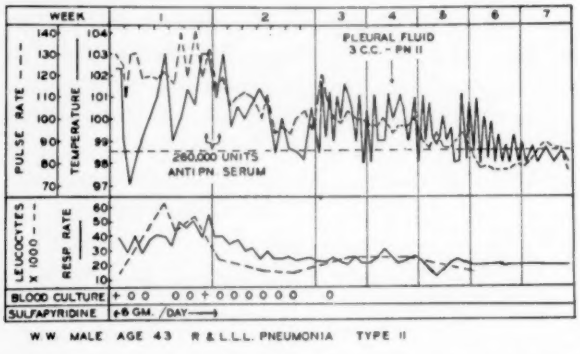

FIGURE 3. *Pneumonia with Bacteremia and an Infected Pleural Exudate, Treated with Sulfapyridine and Serum.*

this patient, the blood had already become bacteria free when the serum was given. One cannot tell with certainty what the course would have been had the serum not been given.

Cases in which failure to respond to chemotherapy was associated with resistance of the pneumococcus to the action of sulfonamide drugs have been described,[4] and it has been shown that in such cases a change from one effective drug to another cannot be expected to be of any help.[4, 5] Such cases do respond in the usual way to the administration of specific antipneumococcus serums. When serum treatment is delayed too long, however, it may prove ineffective.

Figure 3 shows the chart of a patient who illustrates another aspect of the use of serum. The blood was only temporarily rendered free of bacteria under chemotherapy. When serum was administered, the blood was rendered sterile and remained so in spite of the fact that chemotherapy was discontinued. In this patient, the presence of empyema was suspected, but only a small amount of infected fluid was obtained by thoracentesis. Recovery was complete at the time of discharge from the hospital, and surgical intervention was not required. This is another case in which, after serum had been given and the patient had recovered, the specific antibody probably contributed substantially to the recovery, but reasonable doubts may be raised.

The case of A. McL. (Fig. 4) illustrates still another aspect. At the beginning of treatment, this patient seemed to respond favorably; she then had a relapse of symptoms, and the disease failed to respond to further chemotherapy. In this case, organisms could not be cultivated from the blood during the course of chemotherapy, but they were found in large numbers in the sputum. After the end of the second week of treatment, there developed a marked leukopenia, with complete absence of granulocytes in the circulating blood. Angina followed in spite of the fact that the drug therapy was discontinued. The patient responded to transfusions and pentnucleotide injections with a reappearance of granulocytes, but she had an invasion of the blood with Type 8 pneumococcus and died. It is not possible to say that the fatal outcome would have been averted if serum had been given during the first few days. Nevertheless, one cannot help believing that serum should have been given to this patient early during the relapse, making it possible to discontinue the drug and thus possibly to avert the fatal outcome.

The events in this case also serve to emphasize the value of making frequent blood counts in patients who are treated with sulfonamides for more than a week.

Treatment of cases with leukopenia. Because the sulfonamide drugs tend to produce leukopenia

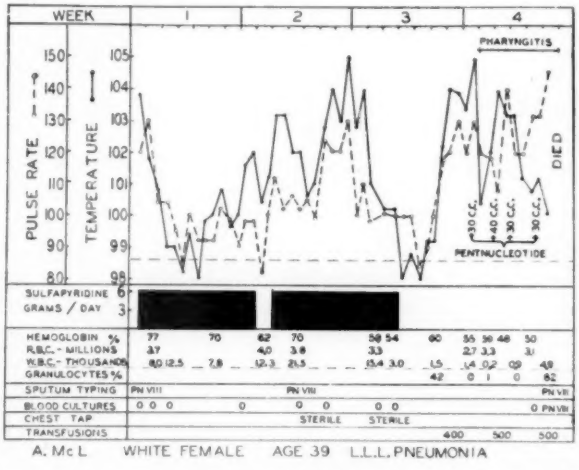

FIGURE 4. *Fatal Agranulocytosis in a Case of Pneumonia Treated with Sulfapyridine.*

and agranulocytosis on prolonged administration, there may be some hesitancy on the part of physicians to give the drugs to patients with low leukocyte counts. It should be emphasized that leukopenia in pneumonia is usually a manifestation of severe infection, and in such cases chemotherapy is definitely indicated. Of course, it must first be ascertained that the leukopenia is not the result of recent therapy with a sulfonamide drug. This is the only absolute contraindication to chemotherapy in the presence of severe infection. Accompanying the leukopenia, there is usually a bac-

teremia. Because of the severity of the disease and the usually slow response in such cases, we believe that serum therapy should also be used.

An example is shown in Figure 5. The patient was extremely ill on admission, and an initial dose of 4 gm. of sulfadiazine was given by mouth. A blood count made at the time of admission

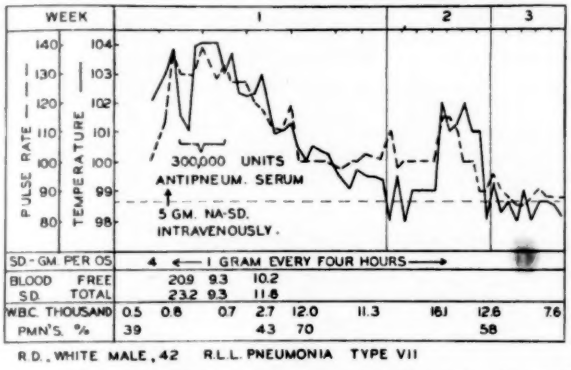

FIGURE 5. *Pneumonia and Severe Leukopenia, Treated with Sulfadiazine and Serum.*

Blood cultures made on admission and again before the first dose of serum were positive; the subsequent ones were sterile.

showed that the patient had a white-cell count of only 500, but there was a moderate proportion of granulocytes. Chemotherapy was discontinued by the house physician on this account, and the results of pneumococcal typing were awaited. However, drug therapy was considered to be indicated, and it was therefore resumed twelve hours later with an intravenous injection of 5 gm. of the sodium salt of sulfadiazine, followed by regular oral doses. Serum therapy was started shortly thereafter. The blood culture was positive on admission and again before the first dose of serum was given. The patient improved rapidly, but the temperature and pulse dropped only gradually during the next two days, after which the white-cell count rose slowly to normal. The role of serum therapy in the recovery is hard to evaluate, but one cannot help believing that it was an important factor.

Blood cultures and bacteriologic studies of the sputum, including sputum typing, are of great help in prognosis and in the conduct of therapy. It is essential to carry these out early if additional serum therapy is to be used successfully.

Some Special Uses of Chemotherapy in Acute Respiratory Infections

It is generally agreed that the present sulfonamide drugs are effective only in infections due to the common pathogenic bacteria and are indicated primarily for the cure of infections with such bacteria. Nevertheless, it is general clinical experience that many acute pulmonary infections respond favorably, although no organisms are recovered that are ordinarily considered etiologic in the disease or susceptible to the drugs.

Primary pneumonias of uncertain etiology. In common with many other observers, we have noted many cases of pneumonia that had all the clinical characteristics of typical lobar pneumonia, both from the history and the physical findings, but cultures of the blood were sterile and examination of the sputum revealed no predominance of pneumococci, hemolytic streptococci, staphylococci or Friedländer's or influenza bacilli. When the simple typing methods are resorted to, reports of "no pneumococci" are the rule. The predominant organism in the sputum cultures is frequently *Streptococcus viridans* or a streptococcus producing only slight (alpha) hemolysis on blood agar. Other organisms, such as *Micrococcus catarrhalis*, may also be found in moderate numbers, and staphylococci or influenza bacilli are sometimes found in small numbers. The organisms found are usually nonpathogenic for mice, but occasionally one of the streptococcal strains may invade the blood of a mouse and give a fatal infection. Many of these cases respond to chemotherapy in the same manner as typical pneumococcal pneumonias. There are other cases with atypical pulmonary consolidation or with x-ray evidence of pulmonary involvement that is considerably more extensive than the physical signs indicate. Some of these cases correspond to the ones that have recently been loosely called "virus pneumonias."[6, 7] Such patients usually fail to respond to chemotherapy in adequate doses.

In the patients who do respond, there is the likelihood that a pneumococcus was the responsible agent but was not recovered in the bacteriologic study. The commonest cause for the failure to identify the pneumococcus is the failure to obtain proper sputum for the bacteriologic examination.

From the practical point of view, it seems worth while to begin chemotherapy in all such cases and to discontinue drugs if after about forty-eight hours there is no definite evidence of improvement in the clinical course. Further treatment subjects these patients to all the possible disadvantages of chemotherapy without offering much hope of beneficial effects.

Secondary pneumonias. We have been much impressed recently with the beneficial effects that may be obtained from chemotherapy in patients with acute pulmonary infections complicating severe and intractable asthma or a severe cardiac failure that does not respond to the usual therapy. The administration of sulfonamides in such cases

is frequently accompanied by a drop in fever and pulse rate, and the underlying disease yields rapidly to proper treatment.

In Figure 6 are shown charts of 7 patients with asthma who had received all the usual therapy for this condition without effect. In each case, there were slight to moderate fever and leukocytosis. The physical signs varied. Some patients had only the usual signs of acute asthma, whereas others had moderate areas of consolidation, particularly in the base of the lungs. The first improvement of the asthma occurred after the patients were given full doses of sulfonamide drugs, and coincided with the drop in fever. These are not cases that are ordinarily included among the pneumococcal pneumonias. In most cases, pneumococci were not recovered, the bacteriology of the sputum was similar to that of the cases just described, and blood cultures yielded no growth.

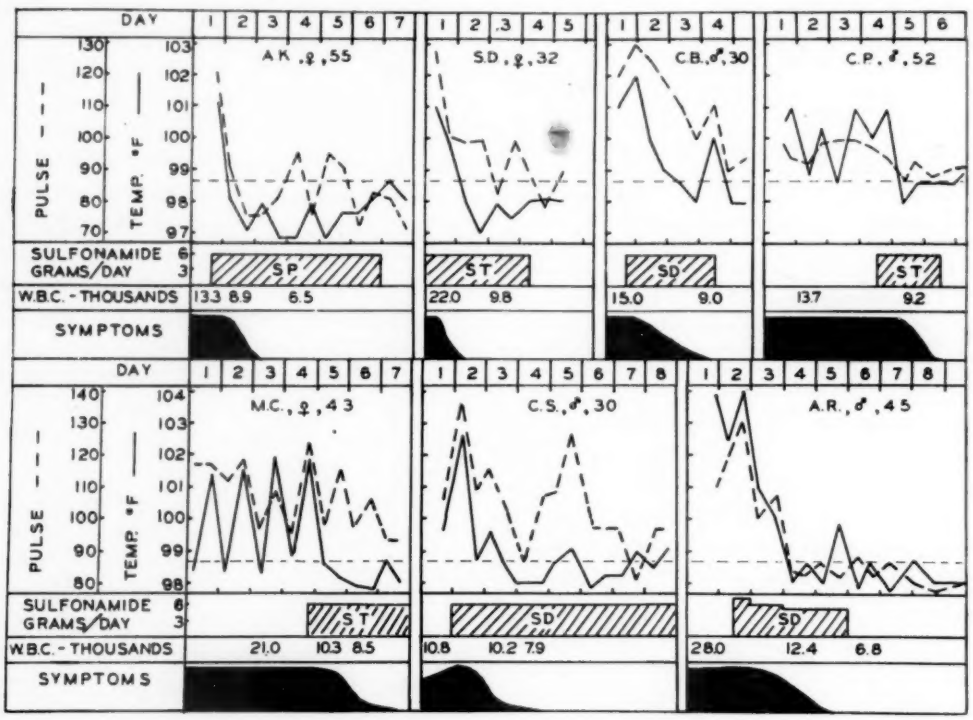

FIGURE 6. *Seven Cases of Severe Acute Bronchial Asthma with Accompanying Acute Pulmonary Infections, Treated with Sulfonamides.*

A group of 3 cases with congestive cardiac failure in which a dramatic response of the cardiac symptoms occurred only after chemotherapy is shown in Figure 7. There was fever in each case. The physical signs may have been attributable to pulmonary congestion or to pulmonary infection. In any event, these signs began to clear soon after sulfonamide therapy was started, and improvement in the symptoms of congestive failure followed rapidly.

In patients with known pulmonary tuberculosis or in others who later prove to have pulmonary tuberculosis, there may occur acute exacerbations in the pulmonary symptoms, with dyspnea, fever, pleural pain, leukocytosis and the appearance of new areas of consolidation in the lungs. In such cases, these signs and symptoms are often due to superimposed bacterial infection, which yields promptly to chemotherapy, leaving the underlying tuberculosis unaffected. Possibly extension of the tuberculosis is averted or limited by such treatment. An example of a case of this sort is shown in Figure 8. The response in this patient was very similar to that usually seen in patients with acute pneumococcal pneumonia. The patient proved to have extensive pulmonary tuberculosis with a positive sputum, but the fever and symptoms subsided rapidly following treatment with sulfapyridine.

The course of events in the last case also serves to emphasize the advantage of following very carefully the fluid intake and output of patients receiving chemotherapy, regardless of the indications for the use of the drug. In this patient, there was a complete suppression of urine at the end of the second day of chemotherapy, after what seemed to be a good response of the acute infection. The patient was given large amounts of fluid parenterally and frequent injections of 50 per cent glucose intravenously without effect. Cystoscopy was performed after sixteen hours. Sulfapyridine crystals

were found in the bladder, in the left ureter and in both kidney pelves; in fact, the left ureter was completely obstructed by clumps of these crystals. Ureteral catheters were inserted into the pelves of the kidneys and kept in place for twenty-four hours, following which the urinary excretion returned to normal.

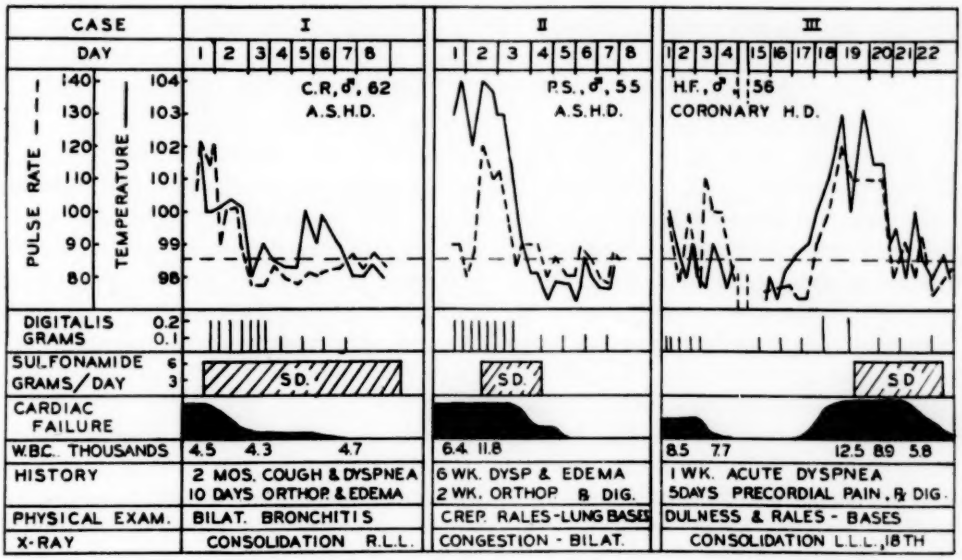

FIGURE 7. *Three Cases of Congestive Cardiac Failure with Fever, Treated with Sulfonamides.*

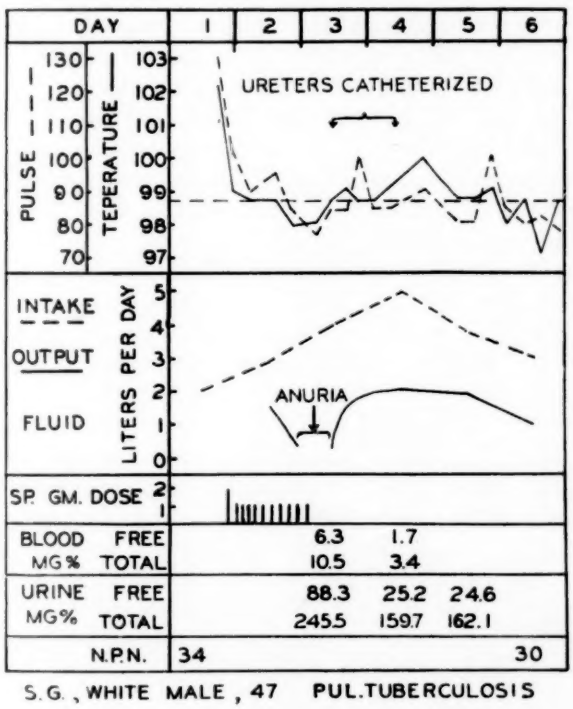

FIGURE 8. *An Acute Febrile Episode in a Case of Pulmonary Tuberculosis.*

The anuria complicating sulfapyridine therapy was relieved by ureteral catheterization.

It should be emphasized that in all these cases the sulfonamide drug was effective in clearing up the acute pulmonary infection. The routine use of sulfonamides in the treatment of asthma, cardiac failure or pulmonary tuberculosis is not recommended. In the absence of definite acute bacterial infection, no beneficial effects are to be anticipated, and the patient is subjected unnecessarily to the treatment. Furthermore, even in the presence of infection, the sulfonamides must be used with great caution to avoid untoward effects. In such cases, sulfonamide therapy should be discontinued in two or three days if the acute infection is not influenced, and should not be maintained for long periods in any event.

* * * *

In this brief presentation, it has been possible to consider only a few of the important problems concerning chemotherapy in pneumonia and to indicate some related situations in which the newer sulfonamides may be of great benefit.

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CARCINOMA OF THE ENDOMETRIUM*

A Review with Results of Treatment Through 1935

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IT HAS seemed to the members of the staff of the Free Hospital for Women that a clearer and broader perspective of our experiences with different forms of cancer is gained if we include in our periodic surveys the cases already reviewed in earlier studies, for longer follow-up gives new information about the survivors and, besides, patients formerly untraceable have in recent years been found in sufficient numbers to change appreciably the previous figures. Furthermore, evaluation of treatment can perhaps be better made by comparing earlier with later results in cases managed in the same clinic because of greater familiarity with the cases and a uniform method of reviewing them.

The present survey, which takes the place of previous publications on this subject from this hospital,[1, 2] the last of which carried five-year results through September, 1927, deals with 307 consecutive previously untreated‡ cases of carcinoma of the endometrium seen from May 1, 1903, through December 31, 1935.§ In every case, the diagnosis was made or confirmed by microscopic examination. For this writing, the pathology has been completely and critically reviewed, with the generous assistance of our pathologist, Dr. Arthur T. Hertig, and, through him as occasion demanded, of Drs. S. Burt Wolbach and Shields Warren.

DATA CONCERNING PATIENTS

The youngest patient in this series at the time of treatment was thirty-three years of age, the oldest, eighty-five. Eighty-four per cent of the patients were over fifty, and 44 per cent over sixty. Forty-one per cent were nulligravidas. Eighty-five per cent had ceased menstruating.

Relevant past history. Three patients had had both ovaries removed fifteen, seventeen and thirty years respectively before admission. At the time of castration, they were all under forty-three years of age. Five had had a radical mastectomy eight months to fourteen years previously. Curettage for abnormal bleeding had been performed on 13 patients five to thirty-three years before entry. A story of x-ray treatments for fibroids and flowing three years and six months to nine years before admission was given by 3. Five patients, 4 of them our own, had been treated successfully by radium (600 to 2400 mg. hr.) for flowing and endometrial hyperplasia, two to nine and a half years previously, and this diagnosis had recently been confirmed for all of them.

Of more immediate significance is the following past history. One patient had been taking ergot for six months for flowing that occurred fourteen years after the menopause. Another had had cysts of the ovaries removed for flowing at the age of fifty-eight, two years before hysterectomy here. A third had had a right salpingo-oöphorectomy for bleeding at the age of fifty-nine, six weeks before admission. Repeated x-ray treatments had been given for flowing to 3 patients for as long as three years without diagnostic curettage. Seventeen women gave a story of curettage one to twenty-four months before admission. Four had had curettage seven to thirty-six months previously, and the tissue had been reported not malignant. Despite persistent flowing, nothing further was done. Thus, about 9 per cent of the whole series had been mismanaged, with resultant delay of proper treatment, if their histories are entirely reliable. If careful examination under anesthesia with curettage of uterine cavity and endocervix and the taking of specimens for biopsy from suspicious areas of the cervix fail to reveal the cause of abnormal bleeding, dogged follow-up is demanded. Recurrence of bleeding thereafter requires immediate hysterectomy, unless a benign cause becomes clearly demonstrable.

General physical examination. As would be expected in a group of women for the most part past middle age, there were many in poor condition. Adequate physical examinations are recorded for 250 of the series, 56 per cent of whom had systolic blood pressures of 150 to 260; 28 per cent weighed 160 pounds or over, the heaviest pa-

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‡During this same period, 15 patients who had had their primary therapy elsewhere received further treatment here. Eight died of recurrence less than five years after first treatment; 2 died of recurrence six to seven years after first treatment; 2 were well at eight and twelve years, having received prophylactic irradiation here; and 3 were well seven, nine and ten years after radium applied here for biopsied vaginal recurrence nineteen to thirty months after hysterectomy elsewhere.

§Omitted from consideration herein are 16 cases so diagnosed prior to May 1, 1903, because no pathological confirmation is available.

tient weighing 276 pounds. Four per cent of the whole series had diabetes; 8 per cent had gallstones, proved by palpation at operation, and this figure is surely low, since the upper abdomen was not explored at every laparotomy and no gallbladder studies were performed on the majority of patients who did not come to abdominal operation. One patient had a duodenal ulcer, and only 1, a nulligravida, had procidentia. Arteriosclerosis was not often recorded, but it must have been rife. This assumption is borne out by the fact that the majority of later deaths not due to recurrent cancer were ascribed to vascular accidents and diabetes.

Treatment

Tables 1, 2 and 3 summarize treatment and results. Removal of tubes and ovaries was included in all the hysterectomies. Thirteen patients were untreated because of hopelessly advanced disease, which was not determined in 9 until exploratory laparotomy. Three of these died postoperatively.

Supravaginal hysterectomy. Obesity, cardiovascular disease, old age, fixation of the cervix and lower uterus deep in the pelvis by inelastic, shrunken supports or by scarring from inflammation and hopeless extension or metastasis, alone or combined, were the usual reasons why only supravaginal hysterectomy was performed on 69 patients of this series. A coring-out of the cervix was included in 19, the first being done as early as 1906. Five of the supravaginal hysterectomies were for other indications in younger women, 4 of whom had early, unsuspected endometrial carcinoma.

Radiation. It was because of operative risk, obviously hopeless disease or both that radiation alone was employed in 36 cases. In the majority, only local palliation was expected. The "cures" by radiation alone were, apparently, the result of two purely chance occurrences, namely, that adequate radiation happened to reach all the growth and that the tumor happened to be radiosensitive. Before 1931, most patients treated by radium alone received single applications of 2400 mg. hr. Three of the 5 surviving five years, however, had had 4800 mg. hr. The capsules of the element in 0.5 mm. of silver were placed, until 1926, in rubber tubing and, until 1931, in brass tubes of 0.5 or 1.0 mm. thickness and inserted into the uterus. Between 1931 and 1935, inclusive, the radium was applied in tubes of 1.0 mm. of brass and 1.0 mm. of lead for totals of 2200 to 4800 mg. hr., these totals being reached in 8 cases by two treatments given two to four weeks apart. Before 1931, x-radiation was given to only 4 patients following operation, in total doses of 600 to 1800 r over a period of weeks. Since the group is so small and the value of the x-radiation as then administered so questionable, the cases are not considered separately.

Preoperative radiation. Until 1931, radiation was not used as a primary treatment in conjunction with operation. Since radium had been of real

Table 1. *Summary of Treatment and Results, Consecutive Cases, May 1, 1903, to 1925, Inclusive.*

Treatment	No. of Cases	Operative Deaths	Status of Patients at Five Years			Status of Patients at Ten Years				Status of Patients at Fifteen Years			
			Untraceable	Dead of intercurrent disease	Alive	Untraceable	Dead of intercurrent disease	Dead of recurrence	Alive	Untraceable	Dead of intercurrent disease	Dead of recurrence	Alive
Untreated	6	1*	0	0	0								
Supravaginal hysterectomy	35	0	2	3	22 (63%)	1	2	3	16 (46%)	2	6	1	7† (20%)
Complete hysterectomy	60	6 (10%)	0	3	38 (63%)	3	2	4	29 (48%)	5	5	1	18‡ (30%)
Radium	12	0	1	0	2 (17%)	0	0	1	1 (8%)	0	1	0	0
Totals	113		3 (3%)		62 (54.8%)			8	46 (40.7%)			2	25 (22.1%)

*Following exploratory laparotomy.

†One patient also had primary carcinoma of the left ovary.

‡In 1 patient, the omentum was resected for a biopsied metastasis at the time of hysterectomy; 1 patient had metastases to the right tube and ovary at the time of hysterectomy; 1 patient had a carcinosarcoma of the endometrium; 1 patient also had in the myometrium a malignant tumor derived from an embryonic rest.

value in 5 of the cases unsuitable for surgery and in some cases with vaginal recurrences, a decision was made to employ it as a supplementary and prophylactic measure before or after hysterectomy. When used preoperatively, the capsules were placed in tandem in a tube of 1.0 mm. of brass and 1.0 mm. of lead from the top of the uterine cavity to or through the external os for a total of 2400 to 3600 mg. hr. Four to seven weeks later, hysterectomy was performed.

The majority of patients receiving radium preoperatively also received x-ray therapy, the rationale being, first, to affect possible metastases or extensions beyond the sphere of radium's influence and, secondly, to reduce perhaps the chances of operative dissemination of the disease without causing in itself significant damage. During the period covered by this report, x-ray therapy was administered by Dr. John W. Meachen, to whom we are grateful for full co-operation. Portals of entry varied from 10 by 10 to 20 by 20 cm.; target distance was 50 cm.; filtration consisted of 0.5 mm. of copper and 1.0 mm. of aluminum; kilovoltage was about 200, and milliamperage 5 to 8. The great majority of individual treatments were of 400 r. Treatments were usually given daily for four days, usually through four portals, two anterior and two posterior. Four treatments totaling 1600 r were given immediately following radium application, and four more after hysterectomy. A few patients received only one series of 1600 r; the majority had a third series of 1600 r six to twelve months after the first for a total of 4800 r. During 1931 and the early months of 1932, some patients received as much as 5400 r in their first two series, the third bringing the total to 7000 r.

There have been, and still are, no definite indications to follow in the selection of cases for pre-

TABLE 2. *Summary of Treatment and Results, Consecutive Cases, 1926 to 1930, Inclusive.*

Treatment	No. of Cases	Operative Deaths	Status of Patients at Five Years: Untraceable	Dead of Intercurrent Disease	Alive	Status of Patients at Ten Years: Untraceable	Dead of Intercurrent Disease	Dead of Recurrence	Alive
Untreated	2		0	0	0				
Supravaginal hysterectomy	20	0	0	4	8 (40%)	0	0	2	6 (30%)
Complete hysterectomy	52	2 (4%)	2	3	35 (67%)	1	3	0	31* (60%)
Radium	8	0	0	1	3 (38%)	0	1	0	2 (25%)
Totals	82		2 (2.4%)		46 (56.0%)		4	2	39 (47.5%)

*One patient had metastasis to a benign pseudomucinous cystadenoma of the right ovary; 1 patient also had a highly malignant sarcoma in a fibroid.

TABLE 3. *Summary of Treatment and Results, Consecutive Cases, 1931 to 1935, Inclusive.*

Treatment	No. of Cases	Operative Deaths	Status of Patients at Five Years: Untraceable	Dead of Intercurrent Disease	Alive
Untreated	5	2*	0	0	0
Supravaginal hysterectomy	5	0	0	1	2 (40%)
Supravaginal hysterectomy, radium, x-radiation (treatments listed according to sequence)	7	0	0	0	7‡ (100%)
Radium, supravaginal hysterectomy, x-radiation	2	0	0	0	1 (50%)
Complete hysterectomy	15	2	0	1	9§ (60%)
Complete hysterectomy, radium	3	0	0	0	2 (66%)
Complete hysterectomy, x-radiation	11	0	0	1	9 (82%)
Complete hysterectomy, radium, x-radiation	26	0	0	2	16 (62%)
Radium, complete hysterectomy	5	1	0	1	3 (60%)
Radium, complete hysterectomy, x-radiation	17	1	0	2	9 (53%)
Radium	12	1†	1	0	3 (25%)
Radium, x-radiation	4	0	0	1	2 (50%)
Totals	112		1		63 (56.2%)

*Following exploratory laparotomy.

†Patient died of acute empyema of the gall bladder 21 days after the first radium treatment (weight 198 pounds, blood pressure 246/130).

‡One patient also had primary carcinoma of the left ovary.

§One patient also had a primary carcinoma of the right ovary.

operative radiation. Some cases were so managed arbitrarily. With a few patients, however, this procedure allowed time to carry out regimens aimed at making them better operative risks. Moreover, when the uterus was considerably enlarged by tumor, it seemed that the shrinkage and drainage resulting from irradiation would facilitate operation. When there was cervical or vaginal involvement, preoperative radiation seemed clearly indicated.

Postoperative radiation. Between the second and tenth weeks of convalescence, a cylindrical "bomb," of 1.0 mm. of brass and 2.0 mm. of lead, containing 100 mg. of radium, was packed transversely across the vaginal vault, and allowed to remain for fifteen to thirty hours, the majority of doses being of 2000 or 2400 mg. hr. Postoperative x-radiation was started within eight weeks of operation, the technic, dosage and timing being as above described. Oftener than not, the first series of x-ray treatments preceded radium application.

Since 1935, combined x-ray and radium therapy has been employed practically routinely before or after operation and for those patients not considered eligible for operation. Radium dosages have been larger, at least 3000 mg. hr. preoperatively or at least 2400 mg. hr. postoperatively, and two applications two to eight weeks apart, totaling 4800 to 6000 mg. hr., for those not operated on. Since the fall of 1937, x-ray treatment, administered by Dr. Richard Dresser, has been given in a single consecutive series. Moreover, regardless of the sequence of therapy elected, an attempt has been made to complete all treatment within eight weeks.

Operative and Pathological Findings

Extent of cancer of the endometrium. In addition to the 13 patients whose disease was considered too extensive for treatment, 4 had vaginal metastases on admission, and 12 had adjacent or distant peritoneal spread. The disease was locally advanced, with fixation of the uterus in 10 cases; in 13 it had reached or grown through the uterine serosa. One patient without extensive local tumor had a presumed liver metastasis. Six cases had apparently localized ovarian metastasis, 1 of which also had a primary carcinoma of the opposite ovary.

Associated malignant tumors. One patient had an axillary recurrence of breast cancer on admission. Another underwent radical mastectomy here for carcinoma of the breast with axillary-node involvement, at which time intrauterine radium was applied as a preliminary to later hysterectomy. There was a concomitant inoperable squamous-cell cancer of the cervix in 1 patient, and in 2, additional pathological study accidentally disclosed very early cancer of the cervix. One patient had four primary tumors — carcinomas of the ovary, cecum, ascending colon and endometrium. In all, 8 patients had a primary carcinoma of the ovary as well as primary endometrial neoplasm. Associated malignant neoplastic disease was present in 3 other patients: a rapidly growing fibrosarcoma of the cervix, a rapidly growing fibrosarcoma in a fibroid and a malignant embryonic rest tumor in the myometrium. Thus, 16 patients, or 5 per cent of the whole series, had more than one primary malignant tumor at the time of entry. Even though the data of this and the preceding paragraph are weighed optimistically, one is forced to conclude that at the very least 15 per cent of the whole series had an obviously poor prognosis when treatment was instituted. As shown in the charts, however, a poor outlook does not necessarily presage a fatal outcome, a fact that helps to maintain optimism in treating this disease.

Other associated pathologic lesions. Pelvic inflammation, chronic or with subacute exacerbation, was present in 45, or 17.4 per cent, of the 258 patients undergoing hysterectomy; fibroids were present in 79, or 30.6 per cent. Diffuse adenomyosis of the uterine wall was found in 5 cases, hemangioendothelioma of the broad ligament in 1 and a carcinoid of the appendix in 1. Benign conditions of the ovary were discovered as follows: pseudomucinous cystadenoma, 3; papillary serous cystadenoma, 3; dermoid, 2; fibroma, 2; endometrioma, 3; beginning papillary cystadenoma, 8; cystadenofibroma, 6; granulosal-cell tumor, 2; thecoma, 2; and bilateral thecoma, 1.

In examining the sections of the ovaries, I was impressed with the frequency of stromal-cell or thecal-cell activity, even to diffuse thecal-cell hyperplasia. Eighty-seven per cent (156 cases) of the available postmenopausal ovaries (180 cases) that were not involved by cancer or benign tumor had what was interpreted as slight to marked thecal-cell activity. One would expect such activity to indicate production of estrogenic hormone, and to be accompanied by corresponding endometrial proliferation, which, however, was not found to any striking degree in the available sections. Sections of endometrium had been prepared from 62 of the postmenopausal cases with apparent activity of the ovarian stroma and showed the following: atrophy, 14; slight proliferation, 35; definite proliferation, 11; and hyperplasia, 2. No correlation between the amount of stromal activity and the amount of endometrial activity was ap-

parent. Of course, the extent of the cancer made it impossible to obtain sections of the endometrium in a greater number of cases and in the above did not allow much choice of area to be sectioned. Moreover, in some cases it seemed that the proximity of the cancer itself gave the endometrium a little stimulation.

The relatively frequent association of endometrial cancer and granulosal-cell tumor appears to substantiate the opinion that continued estrogenic stimulation may carry endometrial hyperplasia on to cancer. The observation of a high percentage of thecal-cell activity in postmenopausal ovaries may perhaps be interpreted as indicating prolonged estrogenic stimulation of a degree insufficient to bring about significant endometrial proliferation, but it also involves the possibility of a reciprocal relation between ovary and endometrial cancer, namely, that the cancer itself may play a part in producing the ovarian change. It should be emphasized that thecal-cell hyperplasia is not in itself peculiar to the ovaries of elderly women with this type of cancer, being seen in various other conditions, but rather that there appears to be more hyperplasia associated with this disease.

Sections of the endometrium had been made from a total of 82 postmenopausal cases. In 62, the ovaries showed thecal-cell activity, as described above, in 12 they were atrophied, and in 8 no ovarian sections had been taken. The endometrial sections from all cases showed the following: atrophy, 22; slight proliferation, 45; definite proliferation, 13; and hyperplasia, 2.

Only 22 cases of the whole series had endometrial polyps, which were found in uteri with less advanced tumor. Many of the cancers themselves hung from the upper uterine cavity as polypoid masses, suggesting origination in a polyp. It is likely that this form of cancer starts in polyps oftener than can be demonstrated.

Tumor pathology. The malignant tumors were typed histologically as follows, the percentage of patients alive at five years being included in parentheses after each group: adenocarcinoma, 161 cases (62 per cent); adenocarcinoma with varying amounts of alveolar massing of undifferentiated cells, 115 cases (49 per cent); adenocarcinoma intermixed with more or less squamous-cell carcinoma, that is, adenoacanthoma, 25 cases (48 per cent); carcinosarcoma, 3 cases (33 per cent); squamous-cell carcinoma, 2 cases (100 per cent); and adenoacanthosarcoma, 1 (0 per cent). This typing is at best only roughly accurate concerning the first two groups, and depends in good part on the number of sections that happened to be taken from different portions of the same tumor. For example, some sections from a tumor appeared to be purely adenomatous, whereas, others from the same tumor showed masses of undifferentiated cells or even areas of squamous-cell cancer. More sections from individual tumors might have changed the classification considerably.

Difficulties were also encountered in attempting to correlate the microscopic degree of malignancy with the duration of symptoms, the gross extent of the disease and the length of survival. It could not be shown that duration of symptoms or microscopic grade of malignancy bore any constant relation to the extent of the disease at the time of treatment or to the length of survival. In the first place, the degree of malignancy often appeared to vary in different areas of the same cancer. Secondly, duration of symptoms involved other factors besides the rate and extent of cancer growth. Some patients with advanced growth had had symptoms for only a short while, owing to cervical or vaginal atresia. Others, with protracted flowing, had highly active tumors still confined within the uterus, which apparently had formed a distensible but impervious barrier. Other cases, with tumors of low microscopical malignancy, had metastases without especially advanced local growth. A rare patient with confined tumor of not too high microscopical malignancy succumbed to exceedingly rapid recurrence without any change in the microscopical appearance of the tumor. Recurrences usually looked more active than the primary neoplasm. In others, whose cancers were of relatively high activity microscopically, the growth of recurrences was slow, sometimes to great size locally, death occurring as late as twelve years and eight months after operation.

Regardless of microscopical malignancy, it is difficult to understand why surgery alone should have cured a case with omental metastasis or with a surface metastasis to an ovary. In such cases, cancer cells must have been more widely disseminated and something must have prevented their "taking." The patients whose clinical courses failed to progress according to prognosis based on operative and pathological findings, for example, rapid recurrence of grossly confined, microscopically low-malignancy cancers or cures despite proved metastasis at the time of treatment, suggest that unknown constitutional factors either enhance or weaken resistance to endometrial cancer or cause the cancer itself to vary greatly in its malignancy, all regardless in general of the microscopic picture.

Results

One hundred and seventy-one patients, or 55.7 per cent of the whole series of 307 cases and 58.1 per cent of the 294 treated cases, were alive at five years. Eighty-five patients, 43.5 per cent of the 195 seen from 1903 to 1930, inclusive, and 45.4 per cent of the 187 who were treated, were alive at the ten-year interval. No attempt has been made to correct the survival figures because of the uncertainty regarding patients who died of intercurrent disease. Without autopsy they may not be considered free of recurrence. To simplify the figures, these and the untraceable patients are rated as dead of recurrence. Because 3 patients died of probable recurrence between twelve and thirteen years after operation, survival for at least thirteen years appears to be the criterion for absolute cure.

Of all the patients treated before 1931, 108 were alive at five years. Five became untraceable, 8 died of intercurrent disease, and 10 died of recurrence before the ten-year interval; 4 were living with recurrence at ten years. Thus, 75 per cent of those alive at five years were known to be alive and apparently free of disease at ten years.

As shown in the tables, the results for the years 1931 to 1935, inclusive, are no better than those of earlier years, despite the fact that 71 cases of this group, 66 per cent of the total treated, had had radium or x-radiation, or both, along with surgery. Forty-seven, 66 per cent, of these 71 patients were alive at five years. With surgery alone, however, practically as good five-year results were achieved. The failure to save more patients of this last group cannot be attributed to any change in operative technic and is probably explained as follows: 32 per cent had, at the time of treatment, extension of the disease, metastasis or another primary malignant tumor, as compared with 17 per cent of the cases listed in Table 1 and 22 per cent of those in Table 2. Although the extra manipulations and the delays attendant on preoperative irradiation have been considered possible factors contributing to the unimproved results, it is more probable that the figures would have been poorer if irradiation had not been given. Furthermore, 6 of these 71 patients died quite definitely of intercurrent disease before five years. Although any advantage of supplementary irradiation cannot be demonstrated unequivocally, it is thought to have been of value. Of possible significance is the fact that only 4 of these, 5.6 per cent, had vaginal recurrence, as compared with 12, 6.3 per cent, of the 187 patients treated by operation only, and all these 4 patients had had advanced growth locally when first treated. Two, 5.5 per cent, of the 36 treated only by irradiation had vaginal recurrence.

Evaluation of irradiation alone in this series may not be made, since it has not been employed in a sufficiently large number of unselected patients.

Operative Mortality and Complications

There were no operative deaths following supravaginal hysterectomy. Four patients developed incisional hernias, and 1 a vesicovaginal fistula, which was easily repaired.

Twelve, 6.3 per cent, of the 189 patients undergoing complete hysterectomy died postoperatively, 6 of pulmonary embolism, 4 of peritonitis and 2 of shock. Three patients developed incisional hernias, and 2 vesicovaginal fistulas, which were repaired satisfactorily.

No deaths or complications could be attributed to the use of radium alone. One death was assigned to the combination of radium and x-radiation:

> Mrs. E. M. I., at the time of complete hysterectomy on August 4, 1931, had metastatic cancer in the posterior vaginal fornix and the pouch of Douglas. Radium, 3000 mg. hr., was applied to the vaginal vault 6 weeks later, following which 2700 r of 200-kv. radiation was given. The same dose of x-rays was administered 2 months later, and 2½ months following this, 2500 r were given, making a total of 7900 r within 6 months. Because of pelvic induration, thought at that time to be recurrent disease, and despite the fact that the patient felt quite well and was gaining weight, another radium treatment (2400 mg. hr.) was given. Increased pelvic induration and stricture of the rectum ensued, with disabling symptoms. Colostomy was performed elsewhere 2 years after operation, and death 8 months later was attributed to cancer of the rectum. From the course so long as followed in this clinic, it is probable that overirradiation caused death.

Severe proctitis without later disability occurred in 2 patients who received, following complete hysterectomy, 2400 mg. hr. of radium, and 7000 r and 4800 r of x-radiation, respectively. No fistulas have yet resulted from the irradiation given. There were only a few cases of transient irradiation cystitis.

Retreatments. Twenty-four patients were treated by radiation for recurrence from a few months to nearly five years after first therapy. Eleven had vaginal, 1 a cervical, recurrence following operation only; 4 had vaginal recurrence after operation in addition to radiation, and there were 2 vaginal and 6 intrauterine recurrences after irradiation only. Only 1 remained permanently cured; 7 lived for six to nearly eleven years from first

treatment; 2 are alive, 1 with recurrence at eight years and six months, and 1 being well at nine years and three months. Recurrence after five years was in every case beyond any hope of palliation by local treatment.

Associated malignant tumors. It is known that 3 of the patients who had had a radical mastectomy before admission had mammary carcinoma. Sixteen more, as described above, had associated primary neoplasms at the time of treatment here. Two patients developed a new primary cancer following treatment of their endometrial cancer. In the first, a carcinoma of the ascending colon was removed two years and six months afterward. She is now well four years and two months after right colectomy. In the second, a primary carcinoma of the urinary bladder was found three years and eight months afterward, despite, or conceivably because of, the irradiation she had had previously. Further radiation and operation were of no avail, and she died fourteen months later. Thus, 21 patients of this series, or 6.8 per cent, had proved multiple neoplasms.

Status of Treatment

From the results presented, it appears that complete hysterectomy, with bilateral salpingo-oöphorectomy and removal of at least a small cuff of vagina, is still the primary desideratum in the treatment of cancer of the endometrium. The operation should include preliminary closure of the external os by suture to prevent possible spill of viable tumor, ligation of the tubal ostia for the same reason immediately on opening the abdominal cavity, and the avoidance so far as possible of direct trauma to the uterus during removal — for example, by applying clamps to the broad ligaments instead of grasping and thereby lacerating the fundus by instruments of traction, for fear of opening up channels of dissemination. These maneuvers have been practiced in the great majority of the complete hysterectomies herein summarized, along with a wide excision of the broad and infundibulopelvic ligaments. The fact that patients die of recurrence in spite of these precautions, even when the tumor is apparently confined within the uterus and the removed tissues show no microscopic metastases, suggests the possibility that the disease may be spread sometimes through uterine veins or lymphatics below the clamped portion of the broad ligaments by the motions necessitated during removal. This consideration intimates that clamping of the whole length of the parametria down to the vaginal vault as early as possible in the operation may be another worthwhile precautionary measure, for the accomplishment of which the vesicouterine flap and bladder would first have to be freed.

Improved results are being reported in small series of cases from the use of radium and x-rays alone. Perhaps if we treated a consecutive series with irradiation alone we could better our results. Of this we are skeptical, for of 24 cases (Table 3) receiving radium with or without x-rays on an average of a little over six weeks before operation, only 4 showed no evidence of the disease in the sections taken from the operative specimens. All had had 2400 to 3600 mg. hr. of radium, and 16 had received 1600 r of x-ray therapy as well. Admittedly, this is about half of what is here considered an adequate dose, but in recent years we have had the same experience with a number of cases in which full irradiation was used. These patients were at first thought unsuitable for operation. Five to fourteen months after full irradiation and general medical measures, a feeling of uncertainty led to operation, and in half the cases cancer was still present. We are not at all convinced that irradiation alone as now administered can supplant surgery in attacking this type of cancer.

Since, however, radium has been lifesaving in some patients with postoperative vaginal recurrence and, alone or with x-rays, has clearly prolonged life, we believe that, combined with x-radiation, it should be employed routinely, either before or after operation. When applied preoperatively, it should be so distributed as to affect the upper vagina as well as the whole length of the uterus.

Summary and Conclusions

A series of 307 consecutive, previously untreated, pathologically confirmed cases of carcinoma of the endometrium seen from May 1, 1903, through December 31, 1935, is reviewed with reference to past history, physical condition, treatment, operative and pathological findings, results, operative mortality, complications, retreatment for recurrence and associated malignant tumors. Previous irradiation for functional uterine bleeding in 8 cases did not inhibit the development of endometrial cancer. According to history, delay of proper treatment, which might have been prevented by the first physician consulted, occurred in 9 per cent of the series. Only 1 patient had procidentia. Five per cent of the series had more than 1 primary cancer at the time of treatment, and 6.8 per cent thus far have had proved multiple malignant neoplasms.

The observation has been made that a high per-

centage of postmenopausal ovaries in cases of this type of cancer show varying amounts of thecal-cell hyperplasia, even to the extent of near-thecoma formation, without, however, commensurate proliferation in the sections of endometrium that were available.

No significant relation could be demonstrated between duration of symptoms, microscopic form or grade of malignancy, extent of cancer at the time of treatment and length of survival.

Of all treated patients, 58.1 per cent were alive at five years. Of those treated before 1931, 45.4 per cent were alive at ten years. Of those living five years after treatment, 75 per cent were known to be alive and apparently free of cancer at ten years. Survival for at least thirteen years appears to be the criterion for absolute cure in this type of cancer.

One death was attributed to overirradiation. The combination of radium and x-radiation produced a few temporary, nondisabling complications.

Of 24 patients treated by irradiation for biopsied local recurrence less than five years after primary therapy, 12 were alive at five years, 2 survived for ten years and 1 was well at fifteen years.

Although in this series irradiation alone has not been employed in a sufficient number of unselected cases to allow proper evaluation, from our experience with patients operated on following irradiation we believe that it cannot supplant surgery.

Preoperative or postoperative application of radium and x-radiation are considered valuable and probably necessary adjuncts to the best management of endometrial cancer, despite the failure to demonstrate in this series unequivocal improvement of results from their use.

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GLAUCOMA AND THE GENERAL PRACTITIONER*

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GLAUCOMA causes about one third of all blindness in patients past middle life. A large percentage of blindness from this cause is preventable by recognized methods of therapy, provided the treatment is begun early. Because physicians in general medicine and surgery can play an important role in the control of glaucoma, this communication is presented.

In this discussion, I shall attempt to explain how glaucoma causes blindness, to review the diagnostic symptoms and signs, to describe briefly the treatment, and to point out how physicians may help in the prevention of blindness from this cause.

Etiology

Glaucoma means an intraocular pressure too high for the eye to withstand safely. Fluid is constantly passing into the eye through the ciliary processes and passing out again through Schlemm's canal. In the normal eye, the intake and outlet of fluid is so beautifully balanced that the intraocular pressure is maintained at a level of about 20 mm. of mercury. In glaucoma, there is either an excessive inflow, or a blockage of the outflow, so that the pressure in the eye rises.

There are various theories concerning the etiology of glaucoma, but this problem is still unsolved. When the pressure in the eye is elevated for a long time, loss of vision results. If the pressure is extremely high, loss of vision is rapid. If the pressure is only moderately elevated, the loss of vision takes place more slowly. In either event, if the intraocular pressure is not controlled, the end result is total and permanent blindness.

Figure 1, which presents a series of visual fields, shows how vision is gradually lost from chronic glaucoma. In this disease, as the field charts indicate, the loss of vision is first in the periphery of the field. In many cases, central vision, or reading vision, is maintained until the disease is in the most advanced stage. Thus, the patient may not be aware of trouble until a large portion of the field of vision is lost.

Glaucoma may be primary or secondary. It is called secondary glaucoma when it is due to some obvious disease of the eye, such as iritis, uveitis, intraocular hemorrhage and certain forms of cataract, or to some operation on the eye, such as that

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for cataract. Although secondary glaucoma is sometimes the more difficult and intractable form, I need not discuss it here, for the patient is usually already in the hands of the ophthalmologist when this complication arises.

Primary glaucoma, which comes on without any obvious cause, is the type considered in this paper. It may be acute or chronic. These two forms are so different in their manifestations as almost to constitute two separate diseases. Figure 2 illustrates the difference between the two types. Thus, in acute glaucoma, the tension between attacks is not merely *almost* normal, but is, in fact, *absolutely normal.* Then comes a sudden rise in tension, to a greater or less degree, depending on the severity of the attack. In the chronic form, on the other hand, although the tension may vary greatly at various times, for practical purposes it can be said that the tension never reaches the normal level. The eye is constantly subjected to various degrees of increased pressure, and this results in permanent structural changes in the eye, especially cupping of the optic disk, which causes a gradual loss of visual field.

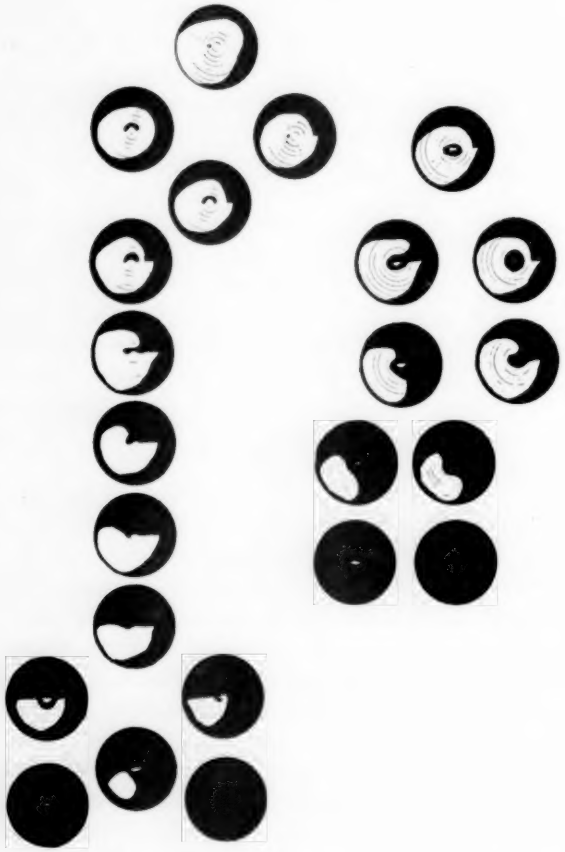

FIGURE 1. *Chart Showing Progressive Impairment of the Visual Field in Untreated, or Inadequately Treated, Chronic Glaucoma.*

Most eyes take the course as shown by the field charts in the left column: here it can be seen that central vision is maintained until a very late stage in the disease. Rarely central vision is lost early, as shown in the field charts in the right column.

SYMPTOMS AND SIGNS

In a typical case of acute glaucoma, there is often a history of mild prodromal attacks. These mild attacks may last from one to several hours; they are characterized by slight to moderate discomfort in the eye and blurred vision of varying degree, and the patient may see colored halos around lights. From such an attack, the patient may recover spontaneously, with the eye symptom free and as good as ever. Then comes the severe attack, from which there is no spontaneous recovery. With this, there is severe, often agonizing pain, rapid and profound loss of vision, and unusually uncontrollable nausea and vomiting. On examining the eye, one finds more or less congestion, a dull steamy appearance to the cornea, a shallow anterior chamber and a pupil that is nearly always partially dilated and fixed. On palpation, the eyeball feels much firmer than that of the unaffected eye.

Acute glaucoma must be differentiated from acute iritis. Severe pain, loss of vision and congestion of the eye may all be manifestations of acute iritis. In cases of iritis, the pain is usually less severe and comes on more gradually, and nausea and vomiting are absent. Aside from actual determination of the tension, the most reliable differential diagnostic point is the size of the pupil, which is larger than normal in glaucoma and smaller than normal in iritis. In acute glaucoma, the terrific pressure in the eye causes a temporary paralysis of the sphincter of the iris, and the pupil becomes larger than normal. In acute iritis, the engorgement and irritation of the inflamed iris cause spasm of the sphincter of the iris, and the pupil becomes smaller than normal.

In chronic simple glaucoma, the symptoms are not of much help in making the diagnosis. The patient may complain of mild pain in the eye, and of periods of blurry vision for hours or days. He may see colored halos around the lights at night. He may complain of seeing poorly in dim light, and of slowness to adapt when going into a darkened room. On the other hand, most patients have no complaints whatever until the disease has reached a relatively advanced stage.

Three signs are of chief diagnostic value: increased intraocular pressure, cupping of the optic disk and characteristic changes in the visual field.

To the well-trained ophthalmologist, the diag-

nosis of chronic glaucoma usually presents no difficulty. The intraocular pressure is accurately measured with a tonometer, the cupping of the disk is recognized by ophthalmoscopic examination, and the visual-field defect is easily mapped out. There is no ocular disease with which chronic glaucoma need be confused.

Treatment

An attack of acute glaucoma should be regarded as an emergency. If adequate treatment is begun within a few hours of the onset of the attack, vision is usually preserved. The later the treatment is begun, and the more inadequate it is, just so progressively worse becomes the prognosis. Forty-eight hours after the onset of the attack may be considered a sort of deadline, for if the beginning of proper treatment is delayed beyond this period, the prognosis is relatively poor.

The ideal treatment consists in lowering the tension to normal with pilocarpine or some other eye drop to constrict the pupil, and a few days later, when the eye is quiet, performing an iridectomy. If this is done, nine such eyes out of ten will remain completely and permanently cured. When the tension has been brought to normal with a miotic drug, both physician and patient may be reluctant to consider an operation. Except in very old patients, I believe that it is a serious mistake not to do an iridectomy, for without it, even with the continued use of drops, further acute attacks are almost certain to occur. It is not known exactly how the operation of iridectomy prevents the attacks in these cases, but the experience of generations has proved its effectiveness.

In many cases, especially if the attack has lasted more than forty-eight hours, it is impossible to lower the tension with pilocarpine or any other miotic. In these cases, operation must be undertaken without delay, even though the operative risk to the eye in the presence of marked congestion and high tension is not inconsiderable and the operation is more difficult to perform. In some of these cases, classic iridectomy may relieve the condition only temporarily, if at all, and further operation may be required. In the late cases, all the efforts of the ophthalmologist may fail.

Aside from the difficulties in satisfactorily lowering the tension in the late cases, there is another even more important reason for instituting early treatment. Eyes vary greatly in their vulnerability to high tension. All ophthalmologists have seen eyes that have been subjected to a high tension for only forty-eight hours and remain totally and permanently blind, in spite of complete relief of the tension. To be sure, most eyes can tolerate a high tension considerably longer than this and still recover part or all the vision if the tension is promptly lowered. However, there is no way of knowing which eyes can tolerate high tension and which cannot. One must act promptly, on the assumption that all eyes are vulnerable to high tension.

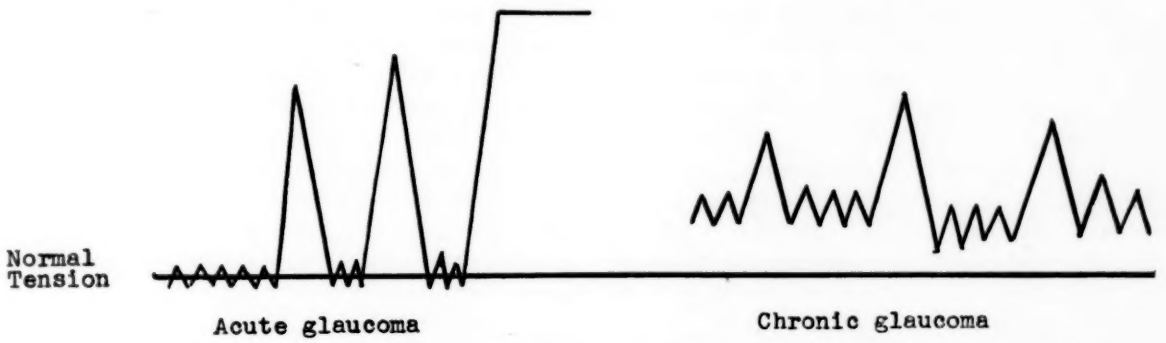

Figure 2. *Diagram Indicating the Differences in Behavior of Intraocular Pressure in Acute and Chronic Glaucoma.*
In acute glaucoma, the tension is always normal, until the sudden rise in pressure during an attack.
In chronic glaucoma, the tension may vary greatly, but is usually above normal.

I have said that it is always advisable, if possible, to lower the tension with miotics before undertaking surgery. There are two points that deserve emphasis. The first concerns the type of drops used and the frequency of their administration. To prescribe 1 per cent pilocarpine three times a day for an eye in an acute attack of glaucoma is like throwing a straw to a drowning man, and about as effective. One should use 4 per cent pilocarpine or 1 per cent eserine, or one of the newer, more powerful miotics, such as Mecholyl and Prostigmine. The drops should be instilled every fifteen minutes for two or three hours, and at least every hour thereafter day and night until the tension is lowered to normal. The

second point in the use of drops is that they must not be relied on too long. A period of twelve hours may be considered an adequate trial. If after this time there is not a substantial lowering of the tension, surgery must be undertaken at once. In patients first seen several days after the onset of the attack, even twelve hours is too long to wait before operation is undertaken.

Chronic glaucoma constitutes no such emergency. Here there is plenty of time carefully to consider the pros and cons of various forms of treatment. The choice of treatment comprises the continued use of a miotic or operation, or both. There is no disease of the eye that calls for such sound clinical judgment concerning correct treatment, as chronic glaucoma does. It is not enough to make the diagnosis and prescribe eye drops to be used two or three times a day. One must be sure that the drops employed bring the tension to, and maintain it at, a sufficiently low level to prevent further damage to the eye. Only when a glaucomatous eye has been observed for some time can one surely say what is the normal tension for *this particular eye*. Some eyes tolerate a pressure up to 30 mm. of mercury without damage, whereas others will show progressive field loss with the pressure maintained at 20 to 25 mm.

In the management of chronic glaucoma, an accurate yardstick with which to measure the effectiveness of treatment is the study of the visual field. No patient suffering from chronic glaucoma is well treated unless periodic measurements of the visual field are made. If loss of visual field continues, treatment, whether it be medical or surgical, has been inadequate. In such cases, whatever the level of the tension, it is too high for this particular eye. The treatment must be revised, or total blindness in the eye will result.

I shall not attempt to discuss the indications for operation in chronic glaucoma. Suffice it to say that the younger the patient the stronger the indication for operation. I believe that most patients under the age of sixty who are in good health and have a normal life expectancy should have operation. Even the most faithful use of drops often fails to hold the disease in check over a period of years. However, each case must be decided on its own merits, and no fixed rules can be laid down. It is not an easy thing for the ophthalmologist to advise surgery on a symptom-free, normally seeing eye. An operation successful in lowering the intraocular pressure may not only fail to improve the vision but may actually lessen it. There is no dramatic restoration of vision here as in the extraction of a cataract. Yet, if one undertakes to treat the disease at all, one must not hesitate to treat it properly.

Prevention of Blindness

General practitioners are often the first to see the patient with acute glaucoma. In every case of severe nausea and vomiting, especially when accompanied by pain in the eye or headache, they should consider this possibility. The patient may be so sick as to forget about the eye and complain only of nausea, vomiting and general prostration. In the early stages, congestion of the eye may be very slight, and may easily escape attention if it is not looked for especially. If there is the slightest doubt whether the case is one of acute iritis or acute glaucoma, it is best not to give any treatment at all. In an attack of acute glaucoma, one drop of atropine may mean the ruin of an eye, for the effect of the atropine is not only deleterious but cannot be overcome by miotics. When the diagnosis has been made, it is the attending physician's responsibility to see that there is no delay in the institution of treatment. The patient may be prostrated by the disease, but he is never too sick to be moved to a place where proper treatment can be carried out. He will never get better until the tension is lowered.

In chronic glaucoma, the physician is not often called on to make the diagnosis. Yet many physicians discover glaucomatous cupping of the disk in routine ophthalmoscopic examination. When the patient has a visual complaint, he should be referred to a physician qualified to diagnose and treat any disease of the eye. The patient should not be permitted to disregard ocular pain, blurred vision, seeing colored rings around lights, poor vision in dim light and slow adaptation to darkness. When a patient who complains of loss of vision is referred to the ophthalmologist, the physician is entitled to an adequate explanation of this symptom. When the diagnosis of chronic glaucoma is made, one can be of considerable help to the ophthalmologist by urging that the patient faithfully carry out the treatment recommended. The patient should be urged to report for the periodic check-ups that are so important in the treatment of this disease. The physician can help more than a little in getting the patient adjusted to the situation: his advice is invaluable in helping the patient to avoid the stresses and strains of life, particularly the emotional strains, which have such a distinctly unfavorable influence on the disease. I may say in passing that glaucoma bears no known relation to any constitutional disease.

Patients past middle life should have a thorough

check-up of their eyes at least once every two or three years. Most cases of chronic glaucoma are discovered in just such routine examinations. A check-up once a year in older people is not too frequent. It makes no difference if they are known to have partial loss of sight from retinal disease or incipient cataract. Glaucoma can coexist with any disease of the eye. The most tragic situation has many times arisen in cases when both incipient cataract and glaucoma are present. The patient may be advised of the presence of the cataract and may watch his vision slowly fail, expecting when he is entirely blind to have his vision restored by cataract extraction. One often has to tell such patients that, true enough, a partial or complete cataract is present, but that all vision has been irretrievably lost from glaucoma. Vision lost from chronic glaucoma can never be restored. One should therefore do everything possible to prevent blindness from this disease.

5 Bay State Road

Discussion

Dr. Charles F. Nutter (Nashua): There is much to learn about glaucoma. Dr. Chandler's exposition of this subject was very clear, but perhaps some of the things he said are not clear to those who are not particularly interested in the disease. Great stress has been properly laid on the increased hardness of the eye. There is pressure on the nerve, which is the weak part of the wall, of course.

Although some ophthalmologists may disagree with me, I have seen cases in which the tension was reduced to normal, but in which progressive blindness occurred, so that later on, the eye was of no use. In those cases, one may be able to find some reason for it. But I believe that some element is present with which we are not really familiar.

Dr. Chandler spoke of the danger of one dose of atropine. I remember a case in which a physician was called to see a patient who had a bilious colic. The pain was not referred to the head; it was underneath the right shoulder blade, extending down into the region of the gall bladder, with every symptom of the passing of gallstones. The patient was given large amounts of morphine and atropine. The next morning, he was totally blind, and remained so, despite all treatment. If you want to give morphine, all right, but leave the atropine out.

One other thing that is very important is the early recognition of glaucoma. I believe that many cases are frequently overlooked, even by ophthalmologists. Consider the large percentage of patients who are wearing glasses, cases of blurring; some of them are at least temporarily blind, and they keep going back to the optometrists or someone who is not legally qualified to make diagnoses. Consequently, many cases of glaucoma get ahead of us. I think that when receiving a prescription for glasses, all patients should be seen by someone who is able to understand and recognize the symptoms of a case of chronic glaucoma.

Dr. Chandler (closing): It is true, as Dr. Nutter said, that we, as ophthalmologists, have a long way to go before we know the answer to glaucoma. Yet the fact is that although we fail in a certain number of cases, there is no excuse for the conception in the mind of the average layman that glaucoma means blindness. I think it is fair to say that in the vast majority of cases, if the diagnosis is made reasonably early, and if the condition is properly treated, the patient with this disease may have useful vision so long as he lives.

MEDICAL PROGRESS

SURGICAL CARE AND OPERATIVE TECHNIC*

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THE current general surgical literature continues to attest to the diversity of modern surgical interests. Much attention is given to such major topics as nutrition, sulfonamide therapy of infections and wound healing. Increased interest in shock and problems of trauma is seen as an inevitable concomitant of war; this was also true in World War I.

NUTRITION

Continued advance in the understanding of the relation between nutritional deficiencies and postoperative complications is evident. As the preoperative condition of the patient is studied more generally and with improved methods, two facts stand out — that nutritional deficiencies are frequently multiple, and that they are often present in latent or subclinical form.[1] Thus, it may happen that unsuspected borderline vitamin or protein deficiency is intensified by the stress of the surgical ordeal and the postoperative period of starvation, with resultant grave complications. The postoperative bleeding of prothrombin deficiency, delayed wound healing or wound dehiscence, malfunction of a gastroenterostomy stoma, postoperative psychosis and liver failure may be taken as illustrative examples.

The importance of the plasma proteins in surgical problems is discussed by Ravdin,[2] who states that it is not only the measurable concentration of the plasma protein that is significant, but also the amount of the reserve or storage protein. Madden and Whipple[3] present the concept of dynamic equilibrium between the body protein stored as a reserve against adversity and the nitrogenous elements in active metabolism. If the exogenous supply of protein is suddenly cut off, the immediate consequences depend on the state of the available reserves. These authors believe that new plasma protein probably flows largely from the liver, although some globulins may be formed elsewhere.

Hartzell, Winfield and Irvin[4] describe their findings in a study of biochemical changes in the plasma of 20 patients at the time of dehiscence of laparotomy wounds. In 14 with dehiscence of clean wounds, the average plasma vitamin C concentration was 0.36 mg. and the serum-protein concentration 5.83 gm. per 100 cc., and the albumin-globulin ratio 1.25; in 6 patients with dehiscence of infected wounds, the respective values were 0.38 mg., 5.84 gm. and 1.30. Average normal values in a group of 20 medical students were found to be 0.96 mg. per 100 cc. for plasma vitamin C and 7.19 gm. per 100 cc. for serum-protein concentration. The authors emphasize the value of correcting deficiency of vitamin C and plasma protein before operation.

In the treatment of hypoproteinemia in surgical patients, Casten and Bodenheimer[5] report that in their experience the administration of massive transfusions of plasma provokes the greatest and most sustained rise in serum proteins. They point out that since the liver holds the key position in maintaining normal stores of plasma protein, all the measures known to favor liver function should be taken, including the administration of carbohydrate, protein and vitamins in adequate amounts. Elman[6] discusses the usefulness of intravenous aminoacid infusions in the correction of protein deficiency. The title of his paper, "Parenteral Replacement of Protein with Amino-Acids of Hydrolyzed Casein," is not free from Hibernicism, since aminoacids cannot substitute for body protein directly, but become protein only through synthetic cellular activity. The usefulness of aminoacid mixtures obtained by enzymatic hydrolysis of casein in the maintenance of nitrogen balance when administered intravenously is receiving confirmation in a number of clinics. In my experience, such therapy is effective even in the presence of severe liver damage.

The occurrence of prothrombin deficiency as a complication of perforative appendicitis and manifested by massive hemorrhages from the operative wound has been reported.[7] It is recommended that in the management of peritoneal sepsis, particularly if it is of gastrointestinal origin, the plasma prothrombin value be determined at frequent intervals and vitamin K be given parenterally if needed. Hypoprothrombinemic bleeding

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may take place in these cases even in the absence of signs of toxic hepatitis and hepatic impairment.

Heparin

Clinical experience is accumulating by which the proper place of this anticoagulant can be estimated. Murray[8] lists the indications for heparinization as follows: arterial suture, excision or repair of arteriovenous fistula, venous grafting, embolectomy and mesenteric thrombosis. In addition, he reports that the prolonged morbidity, discomfort and disability following thrombophlebitis and phlebothrombosis can be reduced by the administration of heparin for four to eight days, as shown in experiences with over 125 patients. He has encountered no cases of pulmonary embolism attributable to the use of heparin, and he rightly points out that heparin has no effect on the established clot. In considering the disadvantages of heparinization, to the drawback Murray mentions — the necessity for immobilizing the patient while he is receiving a constant infusion — may be added the expense, the difficulty in maintaining even and moderate delay in clotting, and the need for frequent determinations of clotting time. Possible interference with inflammatory fixation of bacteria is also to be kept in mind.

Some of the disadvantages of heparin in the maintenance of delayed coagulability in patients may be obviated if further clinical trial supports preliminary observations on the use of a coumarin derivative isolated by Link et al.,[9] of the University of Wisconsin. This substance has recently been identified as the chemical element responsible for the impairment of clotting seen in cattle suffering from the effects of eating spoiled sweet clover. When taken by mouth, the drug inhibits clotting over a period of several days, apparently without other ill effects.

Lehman and Boys[10] report interesting experimental results in the use of heparin in preventing peritoneal adhesions. Their work has been done entirely on animals and does not as yet permit clinical application. They summarize their observations as follows: intraperitoneal heparinization in three daily doses of at least 1000 units largely prevents the re-formation of divided peritoneal adhesions in the dog; hemorrhage following the intraperitoneal administration of heparin is not a danger if hemostasis is complete before the heparin is administered; and contamination of the peritoneum does not appear to be a contraindication to the intraperitoneal use of heparin.

Operating-Room Infections

Continued interest is shown in reducing infection of clean surgical wounds as near as possible to the ideal zero. In a study[11] of the condition of the wound after 606 clean operations, infection of some degree was found in 3.81 per cent, whereas in 1.59 per cent infection was sufficiently severe to prolong the patient's stay in the hospital or endanger life. These figures are probably indicative of the incidence in the average well-run surgical service. Since efforts at further improvement in surgical technic must be directed at the occasional poor result, the challenge here is evident. Hart[12] reports on further experiences with the method he has devised for sterilization of the air in the operating room by bactericidal radiation. He has encountered no untoward results beyond an occasional erythema in members of the operating team who neglected the proper covering. Hart considers the technic to be practical, safe and effective, and states that a significant reduction in wound infection has resulted from its use in his clinic. It should be noted, however, that the method has yet to win approval elsewhere. Rice, Weed and Raidt[13] point out that satisfactory investigation of the bacterial content of the operating-room air can be done only with the air centrifuge of Wells, for the Petri dish method gives misleading results.

Two excellent studies have been reported during the past year on the effectiveness of surgical masking. Hirshfeld and Laube[14] have devised a method for testing masks under conditions of actual use, involving measurements with the Wells air centrifuge. Their most significant conclusion is to the effect that masking of the operating team would be unnecessary if no one talked. They find that the direct spray contamination of talking is greatly reduced when a mask is worn but is still higher than that of quiet breathing without a mask. As tested by their method, the usual four-ply or six-ply gauze mask is grossly inadequate, especially after it has been worn for a while. Rooks, Cralley and Barnes[15] have investigated the value of various types of hospital masks with respect to bacterial filtering efficiency and resistance to air flow. They point out that a completely impervious mask has no value, merely serving as a deflector of the organisms, whereas a highly porous, and hence comfortable, material may have poor filtering power. They find that repeated laundering of masks improves filtering efficiency without proportionate increase in resistance to the breath.

Suture Material and Wound Healing

Judging from the number of reports in the current literature on the use of other suture materials, one would suppose that surgeons are highly dissatisfied with catgut and silk. No less than nine

papers are at hand dealing with the subject. Alloy steel wire has acquired a considerable measure of esteem since its introduction by Babcock in 1932. Jones, Newell and Brubaker[16] state that the substitution of steel wire for catgut has resulted in lowering of the incidence of wound disruption following operations on the biliary tree from 11.0 to 1.2 per cent, whereas the incidence of infection in abdominal wounds after combined abdominoperineal resection and midline colostomy has fallen from 27.5 to 0.85 per cent. They use a series of buried figure-of-eight wire sutures for the peritoneum and rectus sheath, and dispense with stay sutures. In a study by Preston[17] of the tensile strength of skin wounds in white rats sutured with annealed stainless steel wire and with other suture material, the wounds closed with wire had greater strength and showed less local reaction. This author points out that the surgeons' gloves may be torn by the wire ends and that injury to the surgeons' hands in an infected field may occur. Careful technic is essential in using the wire.

Holman and Eckel[18] advocate the use of 20-gauge silver-wire stay sutures in laparotomy wounds. All layers are included, and the separate layers are united with No. 0 chromic catgut. The wire through-and-through sutures are removed in fourteen to sixteen days if no infection is present.

Further experience with the use of cotton thread for suture material tends to confirm original impressions concerning the validity of the technic. Localio and Hinton,[19] on the basis of personal observations, discuss the manner of using cotton thread and the most satisfactory grades and brands. They recommend that cotton thread be sterilized by boiling from ten to twenty minutes and used while wet, for its tensile strength diminishes on drying.

Enthusiastic reports are at hand on the experimental and clinical results of the use of synthetic plastic fiber as buried sutures. According to Aries,[20] Nylon sutures are well tolerated by tendons and nerves, and do not evoke a leukocytic or even lymphocytic response. In infected wounds, Nylon acts much the same as silk in holding the tissues securely and remaining unchanged, and the author concludes that Nylon has all the good qualities of silk and in addition is stronger and less irritating. It may be boiled several times without losing its original strength. Aries recommends a multifilament rather than a monolithic Nylon thread, for although the former evokes slightly more local reaction, it is far easier to handle and the knots are safer and less bulky. Bellas,[21] after using a synthetic plastic-suture material in over 600 wounds, is similarly enthusiastic. In work on guinea pigs and dogs, he finds that remarkably little local reaction is produced by this suture material.

In a careful and well-planned study of factors influencing the tensile strength of healing skin wounds in animals, Botsford[22] finds extracts of spleen and other tissues of no value in accelerating healing. He describes experiments showing the value of secondary suture of wounds, in support of accepted clinical practice. The superiority of silk over catgut is apparent in these investigations, according to the author. In establishing the normal curve of tensile strength of healing skin wounds in guinea pigs and dogs, Botsford notes considerable variation in the ability to heal among supposedly healthy animals and in the individual animal with multiple wounds; these matters should be kept in mind in any consideration of the question of wound healing.

Surgical Operations

Wangensteen[23] vigorously champions aseptic anastomosis in gastrointestinal resections, and presents his experience with the closed method of anastomosis in 100 cases, comprising 83 gastric resections, 14 colonic resections and 3 miscellaneous cases. Only 1 case of postoperative gastric hemorrhage was encountered in the gastric resections, and the author attributes this to the use of the Hofmeister plan of anastomosis, whereby the more vascular part of the stomach is turned in, to ligation of visible subserosal vessels, to the use of a crushing clamp on the stomach and to the use of a coagulating current of the diathermy machine. The author admits that the closed anastomosis results in turning in a wider cuff of poorly approximated visceral wall, but points out that the commonly used Connell stitch is not free from this fault; he apparently does not consider this objection important. The report also includes an exhaustive discussion of details of preoperative and postoperative care. Wangensteen employs a bedside weighing scale in determining the state of hydration of poor-risk patients, a maneuver worthy of wide attention. He uses suction on a forked-type nasogastric catheter to prevent distention of the proximal jejunal loop after gastrojejunal anastomosis, the catheter being manipulated into the ascending and descending jejunal limbs at operation. He concludes that obstruction of the afferent loop in gastrojejunal anastomosis, without gangrene, is a neglected but significant cause of death after gastric resection.

Hoag and Saunders[24] consider the causes of obstruction following gastroenterostomy and sub-

total gastric resection, and propose jejunoplasty as a corrective operation. The procedure embodies the principle of the Finney pyloroplasty on the two limbs of the jejunum at the site of anastomosis, and the incision may be extended to the gastric wall in cases of contracted gastric stoma or marginal ulcer, according to the authors. Although most experienced surgeons have probably resorted to this procedure at one time or another, it is not to be considered the treatment of choice, as Allen notes in his discussion of the presentation. Possible jejunal necrosis and marginal ulceration, as well as the need for considerable operative manipulation in what may be a field of adhesions and inflammation and in what may be a depleted patient, are factors that weigh against routine adoption of jejunoplasty in this connection.

The rapidity of severe depletion in the presence of malfunctioning gastroenterostomy is stressed by Allen and Welch[25] in a comprehensive discussion of this problem. They advise early performance of jejunostomy in the treatment of the condition. The laparotomy wound is reopened for this purpose, and a simple purse-string type of jejunostomy is performed, the catheter being brought out through a stab wound. Provided the nutrition of the patient can be kept in satisfactory state, as by supplying a generous and complete dietary mixture through the jejunostomy tube, their figures show that spontaneous relief of the obstruction can usually be expected.

The use of a vitallium tube in the reconstruction of a strictured common duct is described by Pearse.[26] The tube is flanged, and the ends are flared slightly to fix it permanently in place. Since vitallium is notable for strength, lack of electrolysis and lack of local irritating effects, its superiority over the rubber catheter usually employed for common-duct restoration may establish its place in this connection. As the author hastens to add, the value of such a vitallium tube is problematic if a gap is to be bridged between the ends of the duct.

McKittrick and Warren[27] describe a technical measure that has proved extremely helpful in their experience. As a preliminary to subtotal colectomy and other procedures requiring wide intraperitoneal exposure, the Miller–Abbott tube is passed. The small intestine is thus deflated and threaded on the tube beforehand, and at the operation not only is exposure of the operative field simplified, but the trauma involved in walling off loops of small intestine is obviated.

A point of concern to those interested in the surgery of the biliary tree is dealt with by Brunschwig and Clark.[28] In a case in which resection of the common duct for cancer was being performed, the main hepatic artery was found involved in the growth and had to be ligated and resected. Death of the patient ensued twenty-two days later, from what was thought to be liver failure. At autopsy, there was infarction of the right lobe of the liver, with no peritonitis and no pancreatitis. The authors report that Alessandri in 1937 was able to collect from the literature 10 cases of ligation of the hepatic artery in man, with fatal results in 6 and recovery in 4. He found also that in 18 reported cases in which one of the principal branches of the hepatic artery was ligated, lobar necrosis and early fatality resulted in 7. In man, recovery from ligation of the hepatic artery or its right or left branch apparently depends on the extent of collateral circulation present in the patient.

Carcinoma of the Ampulla of Vater

This difficult surgical problem is now being attacked with a measure of success, made possible by advances in knowledge of the preoperative needs of the jaundiced patients.[29] Orr[30] reviews the 14 reported cases of resection of the duodenum and head of the pancreas for carcinoma of the ampulla, and adds a case of his own to the group. Five of the fifteen patients died after operation without leaving the hospital, and 3 died of metastases, 2 from stenosis of the cholecystgastrostomy stoma, and 1 from bile peritonitis. Four patients were still alive at the time of the report. Although disheartening, these results demonstrate the technical feasibility of excising the lesion, and will undoubtedly pave the way for more successful experiences. The best plan of surgical attack requires further study, bearing on such questions as the choice between one-stage and two-stage procedures, and the optimal type of anastomosis between the obstructed biliary system and the gastrointestinal tract.

Moreland and Freeman[31] point out that two serious complications may follow resection of carcinoma of the ampulla of Vater — fatty degeneration of the liver and cholangitis. The evidence indicates that loss of the external pancreatic secretion can be successfully dealt with by such measures as a low-fat diet and administration of lipocaic, pancreatic tissue or choline. These authors state that a high percentage of tumors in this region are of low-grade malignancy. Occasionally, the growth involving the ampulla is sufficiently localized to permit transduodenal excision, although this method carries with it the danger of inadequate removal of tissue and is therefore not acceptable to surgeons experienced in the treat-

ment of cancer. River, McNealy and Ragins[32] report 3 cases of successful transduodenal excision of periampullary carcinoma, with reimplantation of the common and pancreatic ducts. Two of the patients developed stenosis of the common duct and required subsequent internal biliary drainage. The authors rightly stress the need for carefully determining the condition of the ampulla in operating on any patient with obstructive jaundice, so that no early ampullary growth will be overlooked.

Postoperative Pulmonary Complications

Aspiration bronchopneumonia of varying severity is far commoner after surgical operations than is generally realized, according to Irons and Apfelbach.[33] In fatal cases, the true diagnosis is often missed because of failure to culture lung tissue, tracheal and stomach contents and blood. The characteristic alterations in the pulmonary parenchyma are most readily recognizable if the necropsy is performed within an hour or two of death. Their warning to the surgeon and anesthetist is timely, and points to the need — especially in upper abdominal operations — of preliminary evacuation of the stomach by intubation and maintenance of the head and thorax in a measure of dependency during the operation. In the prevention of postoperative pulmonary complications, Gordon[34] stresses the value of postoperative bronchial drainage by cough, posture or bronchoscopy. He regards bronchoscopy as a safe and simple procedure in well-trained hands, and advises early use of the measure in the treatment of postoperative pulmonary atelectasis.

Lindskog[35] presents clinical and experimental evidence bearing on the etiology of postoperative pulmonary complications. He states that bronchitis, atelectasis and pneumonitis continue to be a source of considerable morbidity and a cause of high mortality, especially in upper abdominal surgery. Lindskog finds that general anesthesia (Avertin) results in an immediate reduction in pulmonary subtidal volume by about 20 per cent before operation. A similar immediate reduction in subtidal volume was observed as a result of operation under local procaine anesthesia with preliminary morphine sedation. His studies led him to postulate a humoral theory for the etiology of postoperative pulmonary complications, according to which histaminelike substances are liberated from the sites of operation; these substances provoke secretion and bronchoconstriction in the lung. The stage is thus set for the action of mechanical factors that increase respiratory embarrassment.

Postoperative Care and Hospitalization

Boyd[36] discusses the formation of renal calculi in bedridden patients, and reports 4 cases in which calcium phosphate stones formed rapidly and required surgical removal. One of the patients was being treated for delayed union of a fractured femur. Measures recommended in the prevention of such stones include acid-ash diet, avoidance of alkali, maintenance of large urine volume and frequent change of position in bed, with emphasis on assuming the prone position when possible.

A recent paper by Leithauser and Bergo[37] reminds me of a remark that the late Dr. E. Amory Codman once made to me on the subject of appendicitis. He predicted that the day would come when interval and prophylactic appendectomy would be performed through a McBurney incision under local procaine anesthesia in the surgeon's office, and the patient would be allowed to go home a few hours later. Leithauser and Bergo discuss their results in a group of 370 cases of appendectomy, in which early rising and ambulatory activity were practiced. The operation was for acute (nonperforative) and chronic appendicitis, and the average period of confinement to bed after operation was 1.5 days. The patients left the hospital by automobile and usually returned on the sixth day for the first dressing. In 66 laparotomies for other conditions, the average time of confinement to bed after operation was 1.9 days; in 18 cholecystectomies, the patients averaged 1.5 days in bed and 8.3 days in the hospital. In the entire group of 436 cases of laparotomy, no wound dehiscence, hernia, pneumonia, thrombophlebitis or other serious complications were observed (except hemorrhage in a gastrojejunal ulcer). The authors used the McBurney incision for appendectomy, and an oblique or transverse incision for cholecystectomy, the wound closure being made with chromic catgut and interrupted, buried steel-wire sutures for the fascia. Their "clinical results suggest the possibility that certain pathologic reflexes originating from the area of mechanical and chemical injury impair respiration and initiate a delay in peripheral circulation which leads to postoperative complications, and that strict confinement to bed favors the development of such complications."

Although few surgeons would care to adopt this program at present, even if it were acceptable to their patients, it must be admitted that the length of confinement to bed and hospital after operation is determined oftener by tradition than by criteria based on careful clinical research. Fur-

ther evidence on this important question should be obtained by studies in a number of clinics.

462 Grider Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27421

PRESENTATION OF CASE

First Admission. A twenty-month-old Italian girl was admitted to the hospital for study.

The child was born at term, weighed 9 pounds, was breast fed for one year, with supplementary feedings after four months, and had been given unspecified amounts of orange juice. She had been well except for occasional coughs and colds until three months before admission, when pallor was noticed. Furthermore, the patient became restless and cried easily, and two weeks before admission, fever and indefinite pains in the hands and stomach were noticed. There had been no vomiting or diarrhea.

The family history was noncontributory. Neither of her two siblings was anemic.

On examination, the patient was well developed but flabby, with puffiness of the hands and feet, and pale, yellow skin. The scleras and mucous membranes were also very pale. The tonsils were large and cryptic; there was no lymphadenopathy. The lungs and the heart were normal except for a soft systolic murmur at the third left interspace. The abdomen was full; the liver was palpable 4 cm. below and the spleen 1.5 cm. below the costal margin. The extremities showed moderate enlargement of the epiphyses.

The urine on numerous occasions showed a + test for albumin and many white blood cells per high-power field. The red-cell count was 1,920,000 with a hemoglobin of 30 per cent, and the white-cell count 21,000 with 54 per cent polymorphonuclears, 36 per cent lymphocytes, 1 per cent monocytes, 7 per cent transitional cells, 21 per cent reticulocytes and 23 per cent nucleated red cells. Smears showed achromia, marked variation in size and shape, and many microcytes and macrocytes. The stools were guaiac negative.

The patient was given a high vegetable and fruit diet with 0.1 gm. of iron citrate each day. The hemoglobin rose to 50 per cent, and the red-cell count to 3,000,000, the smear remaining unchanged. The temperature on one occasion went to 105°F., and this was variously attributed to pyelitis and acute suppurative otitis media. The patient was discharged three and a half weeks after admission.

Final Admission (eighteen years later). In the interval, the patient had been admitted to this and other hospitals on nine occasions, in addition to innumerable visits to the Out Patient Department.

A few months after discharge, the patient was seen again at this hospital, and a diagnosis of lymphatic leukemia made and x-ray treatment given. A year later, she was admitted to another hospital, where an enlarged liver and greatly enlarged spleen were noted, and a von Jaksch's syndrome diagnosed. In a few weeks, the patient was readmitted to that hospital with a temperature of 100°F.; an x-ray film of the chest suggested tuberculosis, and a von Pirquet test was positive. At another institution, the blood was reported to show a red-cell count of 4,180,000 with a hemoglobin of 60 per cent, and a white-cell count of 19,400, with 264,000 platelets and 19 per cent reticulocytes.

At the age of four, the patient had suffered from whooping cough, epistaxis and, later, bronchitis. The following year, a severe epistaxis ("a half cupful") occurred, followed by pain and swelling in both ankles lasting three days. At the last-mentioned hospital, a fragility test showed hemolysis beginning at 0.32 per cent and complete at 0.14 per cent, and an x-ray film of the chest showed the heart and supracardiac shadow to be increased in width. Treatment consisted of 1200 erythema skin units of x-ray.

At six years, the patient was said to have had lobar pneumonia and later during this year was seen at the same hospital complaining of cough and epistaxes of three weeks' duration. On examination she was well developed and nourished, but pale, with the spleen 6 cm. below the costal margin. The red-cell count was 3,700,000 with a hemoglobin of 53 per cent; the white-cell count was 26,500, and the smear as before. Two years later, she developed a prostrating cold and definite scleral icterus, with the liver 4 cm. below the costal margin; the blood picture, however, was slightly improved. At ten years, the icteric index was 20, and a Graham test was negative; some time later, the blood picture was noted to be essentially unchanged. During this period, the patient again contracted lobar pneumonia, and at the age of twelve was readmitted to this hospital complaining of a severe cold and pains in the abdomen and back, of four days' duration. The temperature was 103.6°F., and there were signs of consolidation at the left lung base. A fragility test showed hemolysis between 0.32 and 0.20 per cent. The spleen was not palpable, but following

recovery from the acute infection, both the spleen and the gall bladder, which contained stones, were removed. The spleen weighed 97 gm. and presented an unusual picture. Scattered throughout were numerous foci containing laminated deposits of brownish material, which stained for iron. These were largely enclosed by surrounding fibrous tissue and often showed foreign-body giant cells in contact with these deposits. Extending from these areas, strands of fibrous tissue stretched out and occasionally formed confluent areas of fibrous tissue. There was some increase of the perivascular fibrous tissue, but more marked increase of the perivascular elastic tissue. There was little if any intimal thickening. The lymphoid tissue was markedly reduced, and there was well-marked congestion. Subsequently, a tonsillectomy was performed. The patient was discharged, the blood picture being unimproved.

It had previously been observed that occasional crises occurred during which the patient became more icteric, and the white-cell count and hemoglobin fell to lower levels. She was readmitted to this hospital the same year in one of these crises and complained of headache and fever of five days' duration. On examination, the temperature was 100°F., and the scleras icteric; dental caries were noted, and keloids had developed in the operative scars. The blood showed a red-cell count of 1,900,000 with a hemoglobin of 45 per cent, and a white-cell count of 14,600 with a normal differential. The red cells were as before, with 4 per cent reticulocytes and a large number of normoblasts. Gradually, the blood returned to its old level and did not change over the next two years, despite large doses of iron.

At fourteen, the patient suffered an acute febrile attack accompanied by pain and tenderness in all her joints. This lasted one month, and examination subsequently showed cardiac enlargement, with a continuous thrill in the neck and a continuous murmur in the right second interspace. Both the thrill and the murmur disappeared in dorsal decubitus. A rheumatic nodule was said to have been found in one foot.

For the next five years, the patient remained fairly well and even did light work. One year before her final entry, she was readmitted to this hospital with her stereotyped complaints of fever, cough without sputum and pain in the "stomach." The temperature was 104.6°F., and physical examination suggested right lower-lobe pneumonia. An x-ray film showed evidence of consolidation at the right base, and the heart was still slightly enlarged. The red-cell count was 2,870,000, the hemoglobin 7.5 gm., the hematocrit 18 per cent, the color index 0.9, the mean corpuscular volume 63 cu. microns and the mean corpuscular hemoglobin 26 microgm. Hemolysis began at 0.34 per cent and was complete at 0.14 per cent, control figures running 0.42 and 0.30 per cent, respectively. A sternal biopsy showed erythrogenic hyperplasia, with normoblasts predominating. The patient made a quick recovery on sulfapyridine, but three months later she was readmitted with exactly the same picture, even to the same lobe. The roentgenologist doubted the presence of pneumonia, but a blood culture yielded a Type 4 pneumococcus. The patient again recovered, and following discharge took a course of antipneumococcus vaccine and a course of liver-extract injections. X-ray films of the hands and skull and also those of her sister showed no evidence of erythroblastic anemia.

The patient was finally admitted at the age of twenty, complaining of fever and pallor.

On examination, she was slightly obese and did not appear ill. The skin and scleras were slightly icteric. The heart and lungs were normal, except for fine rales and diminished breath sounds over the right base. The abdomen was normal.

The temperature was 105.8°F., the pulse 120, and the respirations 24.

The urine showed a specific gravity of 1.012, with a ++ test for albumin, and the sediment contained an occasional white blood cell and granular cast per high-power field. The blood showed a red-cell count of 3,300,000 (260,000 of which were sickle-cell forms) with a hemoglobin of 60 per cent, and a white-cell count of 19,300 with 67 per cent polymorphonuclears, 23 per cent lymphocytes, 2 per cent normoblasts and 5 per cent myeloblasts. The serum van den Bergh and blood cholesterol, protein, nonprotein nitrogen and chloride were all normal, and two blood cultures were negative.

X-ray films of the chest showed no evidence of consolidation. There was a widening of the lower dorsal vertebras that was suggestive of an old epiphysitis. Serial films, however, showed the development and progression of an unusual type of pneumonia involving first the left and then both lungs.

The patient was given sulfapyridine, then sulfathiazole, and while she was still on the drug, the temperature rose to 105°F., where it remained for some time. The apex impulse was heaving, and there were runs of bigeminy and trigeminy. An electrocardiogram showed a PR interval of 0.21 second. One observer noted cardiac enlargement and a systolic and a slight apical mid-diastolic murmur, with accentuation of the pulmonic second sound. The right knee became swollen, the right

thumb painful. Finally, dyspnea became more and more severe, and the patient was placed in an oxygen tent. The temperature rose to 106°F., rales developed throughout both lungs, and a pleural friction rub was heard.

Death occurred one month after admission.

Differential Diagnosis

Dr. Thomas Hale Ham*: In summary this is a striking report of an Italian girl who was observed almost every year up to the age of twenty years, when she died apparently from pulmonary disease, which complicated a hemolytic anemia. The features of her clinical course were as follows. She had multiple episodes of hemolytic anemia associated with joint pains or pains in the stomach and frequently with cough and fever. Coincident with several attacks of anemia, she had pulmonary complaints and signs interpreted usually as pneumonia. The laboratory observations revealed an anemia that developed rapidly on numerous occasions and reached a level of 1,900,000 red cells on one occasion. Sickle cells were demonstrated in the blood on her last hospital admission. An increased number of reticulated and nucleated red cells were always present during severe anemia. The red cells were microcytic, with marked variation in size and shape, and showed increased resistance to hemolysis in hypotonic solutions of sodium chloride. Icterus was observed clinically three times, and on one occasion the icteric index was 20. The leukocyte count was consistently elevated. The spleen increased in size from a few centimeters to 6 cm. below the costal margin. Subsequently, it disappeared clinically, and weighed only 97 gm. when removed at operation. The liver was moderately enlarged at all times.

The finding of sickle cells, together with the above evidence, confirms the diagnosis of sickle-cell anemia to explain the blood dyscrasia. Without the pathognomonic observation of sickle-shaped red cells, however, the following types of anemia would require differentiation: sickle-cell, erythroblastic (Cooley's), chronic hypochromic and familial microcytic. Certain distinguishing features[1] of these diseases are shown in Table 1. It is evident that hypochromic and familial microcytic anemia can be excluded because of the presence in this patient of jaundice, splenomegaly, increased reticulocytes and nucleated red blood cells. The distinction between Cooley's anemia and sickle-cell anemia in this case is possible only by the observation of the sickle cells. Otherwise, it might be impossible to differentiate these two diseases, especially since the patient was of Italian parentage. One of the patient's parents must show sickle cells, since this trait is inherited as a Mendelian dominant. Neither parent was tested, however. The occurrence of sickle-cell anemia in white persons has been reviewed recently, with the report of 13 cases occurring in persons from Mediterranean countries, especially Italy.[2] This patient was Italian. The diagnosis of congenital hemolytic jaundice is ruled out in this case by the increased resistance of the red blood cells to hemolysis in solutions of hypotonic saline. There was no history of hemoglobinuria.

The characteristic symptoms of sickle-cell anemia are abdominal and joint pains in half the patients.[3] The predominant physical signs are jaundice and heart murmurs in over 70 per cent of the cases; in about 50 per cent, there is enlargement of the liver and heart; and in approxi-

Table 1. *Distinguishing Features of Several Types of Microcytic Anemia.*

Feature	Sickle-Cell	Erythroblastic (Cooley's)	Chronic Hypochromic	Familial Microcytic
Inheritance of trait	Dominant	Recessive	None	Dominant
Predominant race or nationality	Negro predominately; Mediterranean (Italian) occasionally.	Mediterranean	None	Mediterranean
Morphology of red blood cells	Sickled forms; increased reticulated and nucleated red cells; microcytosis and marked variation in size and shape.	Increased reticulated and nucleated red cells; microcytosis and extreme variation in size and shape.	Less than 5 per cent reticulocytes; microcytosis and moderate to extreme variation in size and shape.	Less than 5 per cent reticulocytes; microcytosis and marked variation in size and shape.
Maximum resistance of red blood cells to hypotonic saline solution	Increased	Increased	Increased	Increased
Icteric index	Frequently elevated	Frequently elevated	Normal	Normal
Splenomegaly	Frequent	Usual	Rare	None
Bone changes	Occasional	Usual	None	Slight changes in skull

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mately one third of the cases there are pathologic changes in the lungs, ulcers or scars on the legs, fever and splenomegaly.[3]

Concerning the pathological physiology of sickle-cell anemia, Hahn and Gillespie,[4] in 1927, demonstrated that the sickled form of the red cells was produced by unsaturation of the hemoglobin by removal of oxygen from the cells. Recent observations,[5, 6] have shown that red cells in the sickled form are strikingly more viscous than normally shaped cells. The viscosity increases as the partial pressure of oxygen is decreased, and the increased viscosity becomes manifest in vitro at about the oxygen tension of mixed venous blood. It is probable that such increases in viscosity occur in a patient with sickle-cell traits and produce a striking degree of stasis in the capillaries. This phenomenon may well account for the infarctions and abnormal destruction of red blood cells observed in certain of these patients.

These physiologic changes agree with observations that capillary blockage is the unit of pathology in sickle-cell anemia.[7] The pathological findings include the presence of sickle cells in dilated capillaries of the spleen, liver, kidney, lung and brain, together with thrombosis and infarction of these organs. The spleen of a child is usually enlarged, the capillaries and pulp being congested with sickled cells. Infarcts are common, and in older subjects the spleen decreases in size with fibrosis and may become extremely small. The lungs may be the site of multiple thromboses and infarcts involving many lobes. Thrombosis involving the brain may be extensive and may cause paralysis in a child as the first sign of sickle-cell anemia.

To return to the case under discussion, it is apparent that the patient had sickle-cell anemia, that the spleen, as described, showed evidence of diminished size, infarction, deposits of hemosiderin, fibrosis and congestion. The lung problem is of great importance, since it probably caused her death. At the age of three years, the child was considered to have tuberculosis, and at the ages of six, ten, twelve, eighteen and twenty the diagnosis of pneumonia was made. The best single explanation for the pulmonary lesion, especially that resulting in the atypical attack of pneumonia during the last illness, is multiple thromboses and infarcts of the lungs. The heart will probably show dilatation without valvular diseases.

Dr. Donald S. King: We were interested in the lungs, and when I saw the patient I thought the diagnoses were Cooley's anemia and acute rheumatic fever. I believed at that time that the joint changes were not associated with the anemia itself. We assumed that this was an atypical pneumonia, probably on a rheumatic basis. I am not at all sure that the pathologist would back that up, since this case was not quite typical of such a pneumonia. This explanation of Dr. Ham's sounds more reasonable.

Clinical Diagnoses

Acute rheumatic fever.
Rheumatic pneumonia.
Cooley's anemia.
Sickle-cell anemia?
Bronchopneumonia.

Dr. Ham's Diagnoses

Sickle-cell anemia.
Fibrosis of spleen, with infarction, deposits of hemosiderin and congestion.
Multiple thromboses and infarcts of lungs.
Dilatation of heart.

Anatomical Diagnoses

Sickle-cell anemia.
Septicemia (hemolytic streptococcus).
Rheumatic myocarditis, probable.
Pericarditis, acute fibrinous.
Acute and chronic pulmonary congestion.
Pulmonary infarcts, multiple.
Hyperplasia of the bone marrow.
Operative scars: sternal biopsy; splenectomy; cholecystectomy.

Pathological Discussion

Dr. Tracy B. Mallory: There is a certain immoral aspect to the diagnosis of this disease, I think, because it is a common observation that if one looks at a fresh sample of blood one may not see sickling, but after delay it may become quite obvious, so that the intern who is slowest perhaps stands the best chance of making the diagnosis. This patient was in this hospital on numerous occasions, at the Children's Hospital several times and at the Huntington Memorial Hospital several times, and only twice in twenty years did anyone notice sickling. Once it was questioned at the Huntington Memorial Hospital, and at the last admission here it was definitely noticed by Dr. Louis Johnson. Several scores of people examined the blood and failed to note sickling. We had a chance to make the diagnosis when splenectomy was done but did not know enough to do it. We recognized at once that this spleen was unlike anything we had seen previously. The pulp looked like the spleen of hemolytic anemia, but there were degenerative changes

in the parenchyma, including foci of fibrosis that one would not expect to see in ordinary hemolytic anemia. The clinicians for the most part thought that the patient must have Cooley's anemia, and at nearly all admissions to this hospital that diagnosis was made. On what basis the diagnosis of lymphatic leukemia was advanced, I do not know. I think it is possible that she may at some time or other have had showers of nucleated red cells, and it is my experience that nucleated red cells are frequently counted as lymphocytes by the average medical intern. I do not know that that was so, but I should strongly suspect it. We eventually sent this spleen to the Johns Hopkins Hospital, where it was looked at by Dr. Arnold R. Rich, who at one glance recognized the lesion as one due to sickle-cell anemia and said it could be nothing else.

The other findings at autopsy are of some interest. The heart was a little dilated but probably not hypertrophic, weighing 300 gm., which is, I think, within normal limits for her age and size. There were no valvular lesions. On microscopic examination, a few small foci of round cells were found in the myocardium. I have backed and filled about these many times, but a few of them are certainly indistinguishable from Aschoff bodies. It seems to me that I must therefore make a diagnosis of active rheumatic fever. There was a fibrinous pericarditis, which may have been rheumatic in origin or may have been due to a terminal hemolytic streptococcus septicemia. The lungs presented a very unusual appearance. They were heavy and extremely red. When they were cut, almost no fluid exuded from them. There were also numerous obvious infarcts. The appearance was very much like that of the most extreme form of chronic passive congestion, the so-called "cyanotic induration of the lung" that one sees with severe mitral stenosis, yet this patient had a normal mitral valve. The infarcts were numerous, and were scattered all over the lung. Most of them tended to be fairly small, 1 to 2 cm. in diameter. The vessels within the infarcts showed thromboses. Elsewhere in the lung, it was very hard to find any thrombi.

An unusual feature about the autopsy was that the blood in all the vessels and in the major chambers of the heart itself was firmly clotted, making it very difficult to decide whether there might or might not have been ante-mortem clots, or whether coagulation had occurred immediately after death, so that ante-mortem clots might easily have been obscured in this extensive post-mortem clotting process.

The picture in the lungs is a little reminiscent of rheumatic pneumonia but not very characteristic, and I think, in view of what Dr. Ham has pointed out to us, that it is much more reasonable to assume it to have been part of the sickle-cell anemia.

The bone marrow was hyperplastic, but to my eye showed no specific changes.

A PHYSICIAN: Would not x-ray treatment have modified the spleen somewhat?

DR. MALLORY: That was what we thought when we originally saw it — that the giant cells could be explained by the fact that radiation had been given. On the other hand, we do not in practice actually see these changes in patients whose spleens have been irradiated. We should have recognized the difference if we had known more about it. To anyone familiar with this disease who happened to think of the possibility, the diagnosis should have been obvious at any time but none of us even thought of it.

Have you any further comment, Dr. Ham?

DR. HAM: The wet-smear method of detecting sickle cells is usually satisfactory, but an immediate result may be obtained by the removal of oxygen from the red cells by equilibration of the blood with carbon dioxide or nitrogen. In this procedure, from 3 to 5 cc. of whole blood is introduced into a 250-cc. tonometer or Erlenmeyer flask equipped with a two-hole stopper. The blood is equilibrated with the gas for ten to fifteen minutes; a small amount of blood is then removed with a pipette, and a drop is placed immediately on a slide under a cover slip. This preparation is then examined for sickle cells. The blood cannot be dried in room air, since the cells are reoxygenated and revert to the nonsickled form.

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The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PHYSICIANS AND CIVILIAN DEFENSE

The recent appearance of a handbook, *Organization Medical Division and Care of Injured Civilians*, issued by the Medical Division of the Massachusetts Committee on Public Safety, emphasizes preparation for civilian defense in America. Whether the plans so well laid will ever have to be called into being, no one can say, but all should be grateful that the Governor has seen fit to establish a mechanism for the protection of civilians. In America, so distant from the shores of Europe, it appears that danger is minimal, but many countries that have thus sought a way out of the effort of preparedness have been guilty of gross misjudgment and have suffered ugly and terrible consequences.

The Public Safety Committee of Massachusetts is composed of five divisions. Two of these, devoted to planning and publicity, are largely auxiliary and do not extend to any degree into the local communities. The Protection Division largely concerns itself with the work of the air-raid wardens and their many different tasks; 10,000 ARP Service men have already been through the schools, and 16,000 are now in training. The Public Services and Supplies Division has spread its network of regional directors and contact men throughout the State; their task deals with the maintenance of power, heat, light, communications, adequate food supplies and so forth. The Health and Social-Services Division has three duties. The Public-Health Section looks after the health of people in preparation for war, the sanitary health measures during an emergency and the health measures that may be necessary after an emergency. The Social-Services Section is concerned with activities promoting better morale, the social conditions in the environments of large army camps, the care of families rendered destitute by a grave emergency and the rehabilitation of individuals and populations after an emergency has passed. The Medical Division* looks after the civilian from the time of injury until his restoration to active life.

The handbook was written to standardize and simplify the medical care of civilian casualties, whether from fire, bombs, bullets or shells, and with certain modifications, the British scheme has been followed. The authority for action when an "incident" occurs rests ultimately in the hands of the chief medical officer of the community. He sends to the scene a squad from the ARP Service. These men, already trained in first aid, enter the demolished houses and remove the injured. The walking wounded are guided, and those severely injured are carried on stretchers to a mobile medical first-aid post, which the chief medical officer has already established at the scene of disaster. Traction splints and bandages are applied, when necessary, and those persons who

*Because of the experience in the recent war games, it has seemed wise to separate the Medical Section from the Public-Health and Social-Services sections, and the Medical Division is now a separate unit.

need hospitalization are immediately transferred by ambulance to the nearest hospital. The patients in hospitals in metropolitan areas are transferred the next day to large base hospitals in the rural districts, such as the Tewksbury State Hospital and various tuberculosis sanatoriums.

The chief medical officer and the local medical committee in each community have the responsibility of setting up these plans. In the large metropolitan areas, it has been suggested that the task be broken down so that one physician organizes the medical first-aid posts, another, ambulance transportation, and another, the hospitals. To assist the chief medical officers, regional directors have been appointed whose areas of jurisdiction largely correspond with those of the district medical societies.

The scheme for this vitally necessary undertaking is reasonable and workable, and is as good as if not better than that devised in any other state. All Massachusetts physicians should gladly and willingly complete the task that has been placed before them.

THE COMMONWEALTH FUND

THE Commonwealth Fund was established in 1918 by Mrs. Stephen V. Harkness to "do something for the welfare of mankind." According to its twenty-second annual report, grants amounting to more than $2,000,000 were given for philanthropic purposes during the past year. A third of this total was devoted to medical research and medical education, and nearly half was contributed to various health services throughout the country, chiefly to rural health departments, and rural hospitals. Grants made in 1940 and in former years for medical research and education amounted to $545,060, a large part being given to thirty-six medical-research projects at sixteen institutions. As an aid to medical education, the fund awarded fellowships for advanced study to seventeen teachers in medical schools. Special assistance was given to the teaching of preventive medicine at the Long Island College of Medicine, New York University College of Medicine, Tufts College Medical School, Tulane University of Louisiana School of Medicine and Vanderbilt University School of Medicine, and to the Department of Psychiatry at the University of Louisville. Other significant contributions went to local public-health services and rural hospitals.

Of particular interest in the current report, however, is the grant of $135,000 to meet special war needs abroad. Gifts were made to the American Red Cross and the British War Relief Society. The Child Guidance Council supported by the fund has proved its usefulness by its work among the children evacuated from London and other cities.

The Commonwealth Fund has indeed adhered to its motto: "To do something for the welfare of mankind." Its indispensable support of numerous efforts to solve the problems of human welfare and happiness and its contribution to the relief of suffering in war-torn Europe echo the motive of the fund's foundation in 1918. Its achievements remain not only a tribute to the selflessness of its founder and the zeal of its directors but also an inspiration to private philanthropy.

OBITUARY

GERALD BLAKE

1880 – 1941

The tradition of medicine was strong and deep in "Jerry" Blake. His father and his brother were doctors. His father was the much beloved Dr. John G. Blake, for many years on the staff of the Boston City Hospital, a fine general practitioner of the old school, who, when he moved to Boston's Back Bay, liked to recall the older days of Boston's South End. His mother was well known to the readers of the Boston *Transcript* under the initials of "M. E. B."

He grew up in a large family, mostly boys. All were gay, with a family talent for singing songs of infectious mirth and of interminable verses. One readily recalls the "Whizz Fish" and the "Bummers Hotel."

In Harvard College, at a time when the Harvard Band was more a manifestation of nearly spontaneous undergraduate enthusiasm than today's expression of nearly musical talent, "Jerry" occasionally beat the bass drum because the band had to have a bass drummer.

In the Harvard Medical School, "Jerry" was the best liked man in the Class of 1905 — friendly,

gay, hard working, intelligent, modest but effective. Family loyalty led him to choose an internship at the Boston City Hospital. He then entered practice in Boston. Of course, with his ability, his integrity and his personality, he was eminently successful professionally. He greatly admired medical research, but his busy, full life of practice gave him no time, and indeed his modesty and his honesty made him feel that he was not fitted for research. In any event, his patients and his family came first.

He went through the various stages on the visiting staff of the Massachusetts General Hospital, and for a number of years held the position of visiting physician. The ward patients loved him for his sympathy, his humor and his excellent care. The interns and residents learned much from him that they had not found in books or laboratories. On ward rounds one morning, an extroverted intern delivered a long dissertation on some topic not particularly related to the patient beside whose bed they had stopped. The patient became very apprehensive over the earnestness of the young man and over the terrifying jargon. He patted the patient and looked kindly at the intern. Finally, he quietly said to the intern, who had paused to get his breath: "What kind of razor do you use? You get a beautiful close shave."

Over a dozen years ago, "Jerry" had a severe tonsillitis. After this, he had albuminuria and a microscopic hematuria, both of which persisted. His blood pressure slowly began to climb. He had two attacks of pulmonary apoplexy, several episodes of minor cerebral accidents and a coronary thrombosis. After the attack of coronary thrombosis, he developed angina, which plagued him daily the last years of his life. He never complained. He insisted on continuing his large active practice, which he did with undiminished excellence. He grew thin because eating gave him angina. I still have the picture of him, tall and thin, slowly shuffling — by this time he had acquired a Parkinsonian syndrome — up the Phillips House steps. "How are you, Jerry?" His face would light up with his old delightful smile, and the answer came, "Oh, fine." And this kept up for months and years, until his complete incapacity made him consent to take his vacation ten days ahead of the time he had stipulated for himself, despite all pleas and protests. On his way to his holiday, he developed his final coronary thrombosis. A great practitioner and a lovable personality had lived a hero for years. "Jerry" had had what it takes to make a hero.

R. I. L.

MEDICAL EPONYM

Koplik's Spots

This sign was described by Henry Koplik (1858–1927) in the *Archives of Pediatrics* (**13:** 918–922, 1896), in an article entitled, "The Diagnosis of the Invasion of Measles from a Study of the Exanthema as It Appears on the Buccal Mucous Membrane."

> . . . . One of the most, if not the most, reliable sign of the invasion of measles has fully failed to receive due attention. . . . If we look in the mouth at this period [during the first twenty-four to forty-eight hours of the invasion], we see a redness of the fauces; perhaps . . . a few spots on the soft palate. On the buccal mucous membrane and the inside of the lips, we invariably see a distinct eruption. It consists of small irregular spots, of a bright red color. In the centre of each spot, there is noted, in strong daylight, a minute bluish white speck. These red spots, with accompanying specks of a bluish white color, are absolutely pathognomonic of beginning measles, and when seen can be relied upon as the forerunner of the skin eruption. . . . As the skin eruption begins to appear and spreads, the eruption on the mucous membrane becomes diffuse. . . . The buccal eruption begins to fade even while the skin exanthema is at its height. . . . In cases where this eruption has been absent, I have always found that my exclusion of a probable attack of measles was correct.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Premature Separation of the Placenta, Followed by Fatal Shock and Hemorrhage

A thirty-year-old para VIII who had been followed adequately during pregnancy began to flow very freely at term, and was consequently sent into the hospital.

The previous seven pregnancies had terminated in normal deliveries.

On entry the patient had a tender uterus and was flowing freely. No mention was made whether the fetal heart was audible. Vaginal examination at this time showed that the cervix was dilated sufficiently to admit two fingers, and no placenta was felt; no treatment was given. Two hours later, a cesarean section was performed, after a diagnosis of premature separation of the placenta had been made. The placenta was found lying free in the uterine cavity, and a stillborn fetus

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section. Letters should be addressed to Dr. Raymond S. Titus, *Secretary*, 330 Dartmouth Street, Boston.

was delivered. The patient's condition was apparently very poor at the end of the operation. She was given intravenous glucose but was not transfused. Four hours after the operation, she died, apparently from shock and hemorrhage.

Comment. This case illustrates quite well how cases of premature separation of the placenta should not be treated. It is a little unusual in prematurely separated placentas to have excessive external hemorrhage; more frequently, external hemorrhage is slight, and internal hemorrhage is great. It would have been very much better to have treated this patient conservatively. She was a multipara, and although not in labor, she certainly had a cervix that was approximately at term, since it is reported that the cervix was dilated to admit two fingers. The conservative treatment would have consisted in tight cervical and vaginal packing, a Spanish windlass, transfusion and small doses of pituitary extract. Frequently, cases of separated placenta are associated with increased blood pressure and albuminuria, but these were not present in this patient. In primiparas when the fetus is still alive cesarean section may be the operation of choice. In these cases, only 1-minim doses of pituitary extract should be used at intervals of approximately an hour until labor is established. The mortality from this complication when so treated has dropped very appreciably, but conservative treatment cannot guarantee against fatality. If the patient is exsanguinated before the treatment is instituted or if she is extremely toxic, with complete suppression of the urine, nothing can prevent a fatal outcome. The shock of an abdominal operation on a patient such as this is often too much for Nature to combat.

MISCELLANY

BOSTON UNIVERSITY SCHOOL OF MEDICINE OFFERS HOSPITALIZATION SERVICE

Hospitalization service will be offered to students of Boston University School of Medicine throughout the present academic year for a five-dollar fee or a donation to the blood bank, President Daniel L. Marsh and Dean Bennett F. Avery of the school recently announced. Under the hospitalization plan, the medical students will receive complete medical care during the school year. The program has been developed under a new agreement, now going into effect with the Massachusetts Memorial Hospitals, to aid medical students needing hospital care throughout the academic year.

NOTE

Dr. C. Sidney Burwell, dean of the Harvard Medical School, recently announced that Dr. Derek E. Denny-Brown, of London, had arrived in Boston from England to take up his duties as professor of neurology and director of the Neurological Unit, Boston City Hospital. Dr. Denny-Brown's appointment dates from September, 1939, but during the interval he has been on leave of absence serving as a major in the British Medical Corps. Since January, 1940, he has been the officer in charge of the Medical Division, Military Hospital for Head Injuries, in England. In his combined duties here he will take active part both in the teaching of medical students and in the care of the sick in the City of Boston.

CORRESPONDENCE

PREMARITAL HEALTH EXAMINATIONS

To the Editor: The Department of Public Health has sent to all Massachusetts physicians a letter describing their responsibilities under the new premarital health-examination law. It is requested that the *Journal* print a list of the laboratories at present approved by the department for performing serologic tests for syphilis, and certain sections of the general marriage laws with which physicians should be familiar.

The blood specimen for serologic examination for syphilis should be sent to the Wassermann Laboratory, 25 Shattuck Street, Boston, or to a laboratory approved by the department. The following laboratories have so far been approved:

Boston
- Beth Israel Hospital
- Boston Health Department
- Leary Laboratory
- Massachusetts General Hospital
- Peter Bent Brigham Hospital

Brockton
- Health Department

Fall River
- Truesdale Hospital

Fitchburg
- Burbank Hospital

Holyoke
- Providence Hospital

Montague
- Farren Memorial Hospital

New Bedford
- St. Luke's Hospital

Pittsfield
- St. Luke's Hospital

Springfield
- Mercy Hospital

Tewksbury
- State Infirmary

Worcester
- City Hospital
- St. Vincent Hospital

Presumably the city laboratories will do blood tests only for local physicians, and the hospital laboratories only those of patients in the hospitals or outpatient departments.

The following sections taken from the Marriage Laws answer most of the questions which marriage applicants will ask physicians:

General Laws, Chapter 207 (as amended):

Section 11. No marriage shall be contracted in this commonwealth by a party residing and intending to continue to reside in another jurisdiction if such marriage would be void if contracted in such other jurisdiction, and every marriage contracted in this commonwealth in violation hereof shall be null and void.

Section 12. Before issuing a license to marry a person who resides and intends to continue to reside in another state, the officer having authority to issue the license shall satisfy himself, by requiring affidavits or otherwise, that such person is not prohibited from intermarrying by the laws of the jurisdiction where he or she resides.

Section 19. Persons intending to be joined in marriage in the commonwealth shall, not less than five days before their marriage, cause notice of their intention to be filed in the office of the clerk or registrar of the town where each of them dwells, or, if they do not dwell within the commonwealth, in the office of the clerk or registrar of the town where they propose to have the marriage solemnized. In computing the five-day period specified in this section and in determining the fifth day referred to in section twenty-eight, Sundays and holidays shall be counted.

Section 20 (as amended by Chapter 127, Acts of 1933). The clerk or registrar shall require written notice of intention of marriage, on blanks furnished by the state secretary, containing such information as is required by law and also a statement of absence of any legal impediment to the marriage, to be given such clerk or registrar under oath, by both of the parties to such intended marriage if both dwell in his town, or, if the parties dwell in the different towns within the state, or if one dwells outside the state, by the party dwelling in his town, or, if both dwell outside the state, by both such parties; provided, that if a registered physician makes affidavit to the satisfaction of the clerk or registrar that a party so required is unable, by reason of illness, to appear, such notice may be given on behalf of such party, by his or her parent or legal guardian, or, in case there is no parent or legal guardian competent to act, by the physician certifying to the illness, or by the other party irrespective of such other party's residence. The oath to such notice shall be to the truth of all the statements contained therein whereof the party subscribing the same could have knowledge, and may be given before the clerk or registrar or before a regularly employed clerk in his office designated by him in writing and made a matter of record in the office. No fee shall be charged for administering such oath. In towns having an assistant clerk or registrar, he may administer the oath.

PAUL J. JAKMAUH, M.D.
Commissioner of Public Health

State House
Boston

NOTICES

BOSTON LYING-IN HOSPITAL

There will be a meeting of the Journal Club of the Boston Lying-in Hospital on Thursday, October 30, at 8 p.m. Dr. Norris W. Vaux, professor of obstetrics at Jefferson Medical College of Philadelphia, will speak on "Some Local Uses of Estrogenic Hormones in Obstetrics and Gynecology."

NEISSERIAN MEDICAL SOCIETY OF MASSACHUSETTS

The annual meeting of the Neisserian Medical Society of Massachusetts will be held on Wednesday, October 29, at 7 p.m., at the Hotel Kenmore, Boston.

PROGRAM

Dinner.
Election of officers.
Speaker: Ernest B. Howard, M.D., director, Division of Genitoinfectious Diseases, Massachusetts Department of Public Health.
Round-Table Discussion: "Gonorrhea and National Defense."

CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the staff of the Carney Hospital will be held in the auditorium of the Carney Hospital on Monday, October 20, at 11:30 a.m.

PROGRAM

Case Reports.
Clinicopathological Conference.
Discussion by Drs. William Flynn, Joseph O'Brien, Norman A. Welch and Roger C. Graves.

Physicians and medical students are invited to attend.

JEWISH MEMORIAL HOSPITAL

A diagnostic therapeutic conference will be held at the Jewish Memorial Hospital on Thursday, October 23, at 11 a.m. Dr. Elliott P. Joslin will speak on "Diabetic Problems."

Interested physicians and medical students are cordially invited to attend.

EDWARD K. DUNHAM LECTURES

The Faculty of Medicine of Harvard University has announced that the following lectures, prepared by Dr. Rudolf Schoenheimer, formerly associate professor of biological chemistry, Columbia University College of Physicians and Surgeons, will be delivered by Professor Hans T. Clarke, under the Edward K. Dunham Lectureship for the Promotion of the Medical Sciences:

Tuesday, October 28. The Chemical Reactions of the Body Fats.
Wednesday, October 29. The Chemical Reactions of the Body Proteins.
Thursday, October 30. The Dynamic State of the Body Constituents.

These lectures are scheduled for 5 p.m. at the Harvard Medical School, Amphitheater, Building C.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular monthly meeting of the New England Society of Physical Medicine will be held on Wednesday evening, October 22, at the Hotel Kenmore, Boston.

The council will meet at 6:00, and an informal dinner will be held in the Empire Room at 6:30. At 8:00, Dr. Augustus Thorndike, Jr., will speak on "The Effects of Physical Therapy on Athletic Injuries."

All members of the medical profession are cordially invited to attend.

CUTTER LECTURE

Sir William Wilson Jameson, chief medical officer, Ministry of Health, London, will give the Cutter Lecture on Preventive Medicine at the Harvard Medical School on Wednesday, October 22. His subject will be "Public Health in Britain at War," and the lecture will begin at five o'clock in the amphitheater of Building E. These lectures have been given annually since 1912. The medical profession, medical and public-health students and others interested are invited to attend.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse, under Alexander Thiede, every Thursday at 8:30 p.m. at Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, 520 Beacon Street, Boston (KEN 3200 or LON 2155).

THOMAS WILLIAM SALMON MEMORIAL LECTURES

The Salmon Committee on Psychiatry and Mental Hygiene invites the members of the medical profession and their friends to the ninth series of Thomas William Salmon Memorial Lectures.

This series will be given by Dr. Robert D. Gillespie, psychiatric specialist of the British Royal Air Force. The lectures will be given on November 17 and 18 in New York City, November 19 in Toronto, November 21 in Chicago, November 22 in New Orleans, November 27 in San Francisco and November 30 in Philadelphia. Dr. Gillespie will speak on "Psychoneuroses in Peace and War, and the Future of Human Relationships."

MASSACHUSETTS PUBLIC HEALTH ASSOCIATION

A meeting of the Massachusetts Public Health Association will be held at the Commander Hotel, Cambridge, on Thursday, October 30.

The section meetings will be held at 3 p.m. A buffet supper ($1.25 per cover) will be served at 6 p.m. Following the general business meeting at 7 p.m., seven experts will conduct a symposium, "New Developments in Prophylactic Immunizations."

RECEPTION FOR DR. HYMAN MORRISON

A reception and tea in honor of Dr. Hyman Morrison will be given October 19, at 2:30 p.m., at the Beth Israel Hospital, celebrating his sixtieth birthday. A sum of money has been collected for the purpose of establishing the Hyman Morrison Laboratory for Research in Medicine at the National University, Jerusalem. A check for this purpose will be presented to Dr. Morrison on this occasion.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, October 19

Monday, October 20

*11:30 a.m. Monthly clinical meeting and luncheon of the staff, Carney Hospital auditorium.

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

Tuesday, October 21

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. The Physician in National Defense. Dr. Donald E. Currier. South End Medical Club, headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

Wednesday, October 22

*9:00–10:00 a.m. Acne, Hirsutism and Menstrual Disorders. Dr. C. H. Lawrence. Joseph H. Pratt Diagnostic Hospital.

10:00 a.m. John T. Bottomley Society. Carney Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

*5:00 p.m. Public Health in Britain at War. Sir William Wilson Jameson. The Cutter Lecture. Harvard Medical School, amphitheater of Building E.

*8:00 p.m. The Effects of Physical Therapy on Athletic Injuries. Dr. Augustus Thorndike, Jr. New England Society of Physical Medicine, Hotel Kenmore, Boston.

Thursday, October 23

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m. Diabetic Problems. Dr. Elliott P. Joslin. Jewish Memorial Hospital.

Friday, October 24

*9:00–10:00 a.m. Physical Fitness in Late Maturity. Dr. Robert T. Monroe. Joseph H. Pratt Diagnostic Hospital.

Saturday, October 25

*9:00–10:00 a.m. Presentation, with discussion, dispensary and district cases. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

October 13–24. 1941 Graduate Fortnight of the New York Academy of Medicine. Page 834, issue of May 8.

October 17. New England Society of Psychiatry. Page 600, issue of October 9.

October 19–23. American Academy of Ophthalmology and Otolaryngology. Page 350, issue of August 28.

October 28–30. Edward K. Dunham Lectures. Page 635.

October 29. Neisserian Medical Society of Massachusetts. Page 635.

October 29–30. New England Postgraduate Assembly. Pages vi and vii.

October 29–November 1. Association of Military Surgeons. Page 473, issue of September 18.

October 30. Journal Club meeting, Boston Lying-in Hospital. Page 635.

October 30. Massachusetts Public Health Association. Notice above.

November 3–7. American College of Surgeons. Page vii, issue of July 31.

November 5–6. American Conference on Industrial Health. Page 473, issue of September 18.

November 13. Pentucket Association of Physicians.

November 17–19, 21–22, 27 and 30. Thomas William Salmon Memorial Lectures. Notice above.

January 3. American Board of Obstetrics and Gynecology. Page 473, issue of September 18.

January 10–11. Forum on Allergy. Page 392, issue of September 4.

April 6–10. American Congress on Obstetrics and Gynecology. Page 600, issue of October 9.

April 20–24. American College of Physicians. Page 996, issue of June 5.

(Continued on page xii)

For the local Treatment of Acute Anterior **Urethritis**
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1. Knight, F., and Shelanski, H. A., "Treatment of Acute Anterior Urethritis with Silver Picrate," Am. J. Syph., Gon. & Ven. Dis., 23, 201 (March), 1939.

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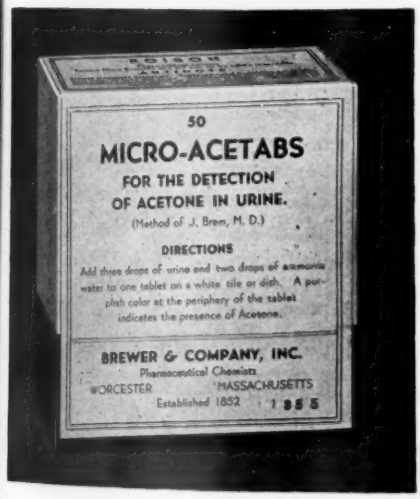

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SOLE IMPORTER

District Medical Societies

BERKSHIRE
- October 30.
- April 30.

BRISTOL NORTH
- April 16. Taunton.

ESSEX NORTH
- January 7. Haverhill.
- May 6. Lawrence.

ESSEX SOUTH
- November 12. Beverly Hospital, Beverly.
- December 3. Salem Hospital, Salem.
- January 7. Danvers State Hospital, Hathorne.
- February 11. Lynn Hospital, Lynn.
- March 4. Essex Sanatorium, Middleton.
- April 1. Addison Gilbert Hospital, Gloucester.
- May 13. Annual meeting (place to be announced).

FRANKLIN
- November 11.
- January 13.
- March 10.
- May 12. Annual meeting.
- Meetings will be held at the Franklin County Hospital at 11:00 a.m.

HAMPSHIRE
- November 5. Veterans Hospital, Leeds, 4:30 and 6:00 p.m.
- January 7. Belchertown State Hospital, 1:00 and 4:00 p.m.
- March 4. Hotel Northampton, Northampton, 4:30 and 6:30 p.m.
- May 6. Hotel Northampton, Northampton, 8:30 p.m.

MIDDLESEX EAST
- November 12.
- January 28.
- March 18.
- May 6.

All meetings will be held at 12:15 p.m. at the Bear Hill Golf Club, Stoneham, except that of May 6, which will be held at Woburn at 6:30 p.m.

MIDDLESEX NORTH
- October 29.
- January 28.
- April 29.

NORFOLK SOUTH
- November 6.
- December 4.
- January 8.
- February 5.
- March 5.
- April 2.
- May 7.

All meetings will be held at 12:00 noon at the Norfolk County Hospital, South Braintree, with the exception of that of February 5, which will be held at the Quincy City Hospital, Quincy.

PLYMOUTH
- November 20. Plymouth County Hospital, South Hanson.
- January 15. Brockton Hospital, Brockton.
- February 19. Jordan Hospital, Plymouth.
- March 19. Goddard Hospital, Brockton.
- April 16. Bridgewater State Farm, Bridgewater.
- May 21. Lakeville Sanatorium, Middleboro.

SUFFOLK
- October 22. Page 559, issue of October 2.
- April 29. Annual meeting. 8:15 p.m., Boston Medical Library.

WORCESTER
- November 12. Grafton State Hospital, North Grafton.
- December 10. Worcester City Hospital, Worcester.
- January 14. St. Vincent Hospital, Worcester.
- February 11. Worcester State Hospital, Worcester.
- March 11. Memorial Hospital, Worcester.
- April 8. Hahnemann Hospital, Worcester.
- May 13. Annual meeting, Worcester Country Club, Worcester.

WORCESTER NORTH
- October 22. State Hospital, East Gardner.
- January 28. Leominster Hospital, Leominster.
- April 22. Burbank Hospital, Fitchburg.
- July 22. Henry Heywood Memorial Hospital, Gardner.